

CANNABIS

PEER REVIEW

1964-2016

Over 650 Peer Reviewed Reports & Studies On Cannabis

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Health benefits, cancer fighting qualities and many other medicinal advantages can be attributed to the Cannabis Plant. Likewise, diseases and disorders are also related to smoking, vaping and ingesting components of the Cannabis Plant. Cannabis users should be aware and well informed regarding both the positive effects and the negative consequences of regular Cannabis use and this eBook accomplishes that goal by employing over 400 current peer reviewed reports and studies—their findings—with active hyper links to each report.



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Eliminate Plastic Products From Your Life
And Eat Organic!



Smoking anything at all is unhealthy

INTRODUCTION

Increasing prevalence of recreational cannabis use among the young population has stimulated debate on the possible effects of acute and longterm use.

Cannabinoids derived from herbal cannabis interact with endogenous cannabinoid systems in the body. Actions on specific brain receptors cause dose-related impairments of psychomotor performance with implications for car and train driving, aeroplane piloting and academic performance. Other constituents of cannabis smoke carry respiratory and cardiovascular health risks similar to those of tobacco smoke.

Cannabis is not, as widely perceived, a harmless drug but poses risks to the individual and to society.

Herbal cannabis contains over 400 compounds including over 100 cannabinoids, which are aryl-substituted meroterpenes unique to the plant genus Cannabis. The pharmacology of most of the cannabinoids is largely unknown but the most potent psychoactive agent, Δ^9 -tetrahydrocannabinol (Δ^9 -THC, or THC), has been isolated, synthesised and much studied.

Other plant cannabinoids include Δ^8 -THC, cannabidiol and cannabidiol (Fig. 1, Table 1). These and other cannabinoids have additive, synergistic or antagonistic effects with THC and may modify its actions when herbal cannabis is smoked. Synthetic cannabinoids such as nabilone and others are also available for therapeutic and research purposes. Non-cannabinoid constituents of the plant are similar to those found in tobacco (with the exception of nicotine).

Cannabinoids are present in the stalks, leaves, flowers and seeds of the plant, and also in the resin secreted by the female plant. The THC content varies tremendously between different sources and preparations of cannabis (Table 2). Over the past 20 years, sophisticated cultivation (such as hydroponic farming) and plant-breeding techniques have greatly increased the potency of cannabis products. In the 'flower power' days of the 1960s and 1970s an average reefer contained about 10 mg of THC.



Now a joint made out of skunkweed, netherweed and other potent subspecies of *Cannabis sativa* may contain around 150 mg of THC, or 300 mg if laced with hashish oil. Thus, the modern cannabis smoker may be exposed to doses of THC many times greater than his or her counterpart in the 1960s and 1970s (Mendelson, 1987; Gold, 1991; Schwartz, 1991; World Health Organization, 1997; Solowij, 1998).

This fact is important since the effects of THC are dose-related and most of the research on cannabis was carried out in the 1970s using doses of 5-25 mg THC (World Health Organization, 1997). Gold (1991, p. 356) remarks: "This single fact has made obsolete much of what we once knew about the risks and consequences of marijuana use".

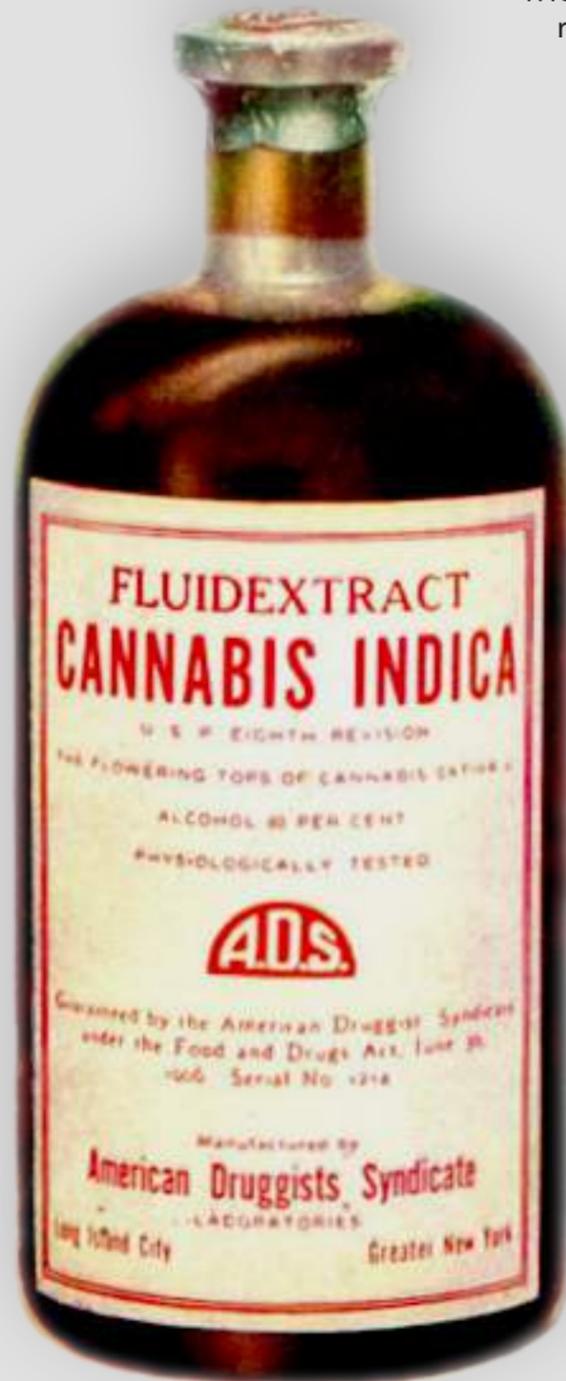
In the UK at present, many recreational users grow their own supplies of high-potency cannabis (exact details of how to grow it can be obtained on the internet). Another main source is imports from Holland (also high-potency) and home growers can obtain seeds in Amsterdam at £10-£50 for 10 seeds, depending on potency. Cannabis can be smoked as joints, from pipes, or from 'buckets', by inhaling from a mass of plant or resin ignited in a sawn-off plastic bottle. It can also be eaten, baked into cookies or cakes or occasionally drunk as an extract. It is unsuitable for intravenous use as it is relatively water insoluble, although it has been dissolved in alcohol and delivered as a fast-flowing saline infusion for research purposes.

PHARMACOKINETICS OF CANNABINOIDS

The pharmacokinetics of cannabinoids are reviewed by Agurell et al (1986) and Maykut (1985) and others. About 50% of the THC in a joint of herbal cannabis is inhaled in the mainstream smoke; nearly all of this is absorbed



through the lungs, rapidly enters the bloodstream and reaches the brain within minutes. Effects are perceptible within seconds and fully apparent in a few minutes. Bioavailability after oral ingestion is much less; blood concentrations reached are 25-30% of those obtained by smoking the same dose, partly because of first-pass metabolism in the liver. The onset of effect is delayed (0.5-2 hours) but the duration is prolonged because of continued slow absorption from the gut. Once absorbed, THC and other cannabinoids are rapidly distributed to all other tissues at rates dependent on the blood flow (Fig. 2). Because they are extremely lipid soluble, cannabinoids accumulate in fatty tissues, reaching peak concentrations in 4-5 days. They are then slowly released back into other body compartments, including the brain. Because of the sequestration in fat, the tissue elimination half-life of THC is about 7 days, and complete elimination of a single dose may take up to 30 days (Maykut, 1985). Clearly, with repeated dosage, high levels of cannabinoids can accumulate in the body and continue to reach the brain. Within the brain, THC and other cannabinoids are differentially distributed. High concentrations are reached in neocortical, limbic, sensory and motor areas.



Cannabinoids are metabolised in the liver. A major metabolite is 11-hydroxy-THC which is possibly more potent than THC itself and may be responsible for some of the effects of cannabis. More than 20 other metabolites are known, some of which are psychoactive and all of which have long half-lives of several days. The metabolites are partly excreted in the urine (25%) but mainly into the gut (65%) from which they are reabsorbed, further prolonging their actions. Because of the pharmacokinetic characteristics of cannabinoids — both the sequestration in fat and the presence of active metabolites — there is a very poor relationship between plasma or urine concentrations and degree of cannabinoid-induced intoxication.

Cannabinoids exert their effect by interaction with specific endogenous cannabinoid receptors, discovered by Devane et al (1988). Neuronal cannabinoid receptors are termed CB1 receptors and have been found in rat, guinea pig, dog, monkey, pig and human brains and peripheral nerves. A second cannabinoid receptor, the CB2 receptor, was identified by Munro et al (1993) in macrophages in the spleen and is also present in other immune cells. The distribution of CB1 receptors is very similar to that of injected THC and includes cerebral cortex, limbic areas (including hippocampus and amygdala), basal ganglia, cerebellum, thalamus and brainstem (Herkenham, 1995).

The discovery of cannabinoid receptors naturally stimulated a search for an endogenous ligand with which the receptors naturally interact. Such a substance was isolated from the pig brain by Devane et al (1992). It was found to be chemically different from plant cannabinoids: it is a derivative of the fatty acid arachidonic acid (arachidonyl ethanolamide) related to the prostaglandins (Fig. 3). This endogenous substance was named anandamide after the Sanskrit word for bliss, ananda. It has a high affinity for CB1 receptors and has most of the actions of THC. Thus, the story of opium, opioid receptors and endogenous opioids is now repeated with cannabis, cannabinoid receptors and anandamides.

Two similar endogenous fatty acids have since been isolated (Fig. 3) and it now appears that there may be a whole system of multiple cannabinoid receptors and anandamide-related substances. Their physiological function has yet to be elucidated (see Pertwee, 1995, for a review). It appears that both anandamides and their receptors reside within neuronal lipid membranes and act as neuromodulators through intracellular G-proteins controlling cyclic adenosine monophosphate formation and Ca²⁺ and K⁺ ion transport. In this role the system may have important interactions with other neurotransmitters, including γ -aminobutyric acid, opioid systems and monoamines. In particular, THC has been shown to increase the release of dopamine from the nucleus accumbens and prefrontal cortex (Tanda et al, 1997). This effect, which is common to many drugs of misuse (including heroin, cocaine, amphetamine and nicotine), may be the basis of its reinforcing properties and its recreational use. It is reversed by naloxone, suggesting an opioid link.

ACTIONS OF CANNABIS IN HUMANS

Cannabis affects almost every body system. It combines many of the properties of alcohol, tranquillisers, opiates and hallucinogens; it is anxiolytic, sedative, analgesic, psychedelic; it stimulates appetite and has many systemic effects. In addition, its acute toxicity is extremely low: no deaths directly due to acute cannabis use have ever been reported. Only a selection of cannabis effects are described in this review; other actions are reviewed by Paton & Pertwee (1973), Pertwee (1995), Adams & Martin (1996) and many others.



Psychological effects

Effect on mood

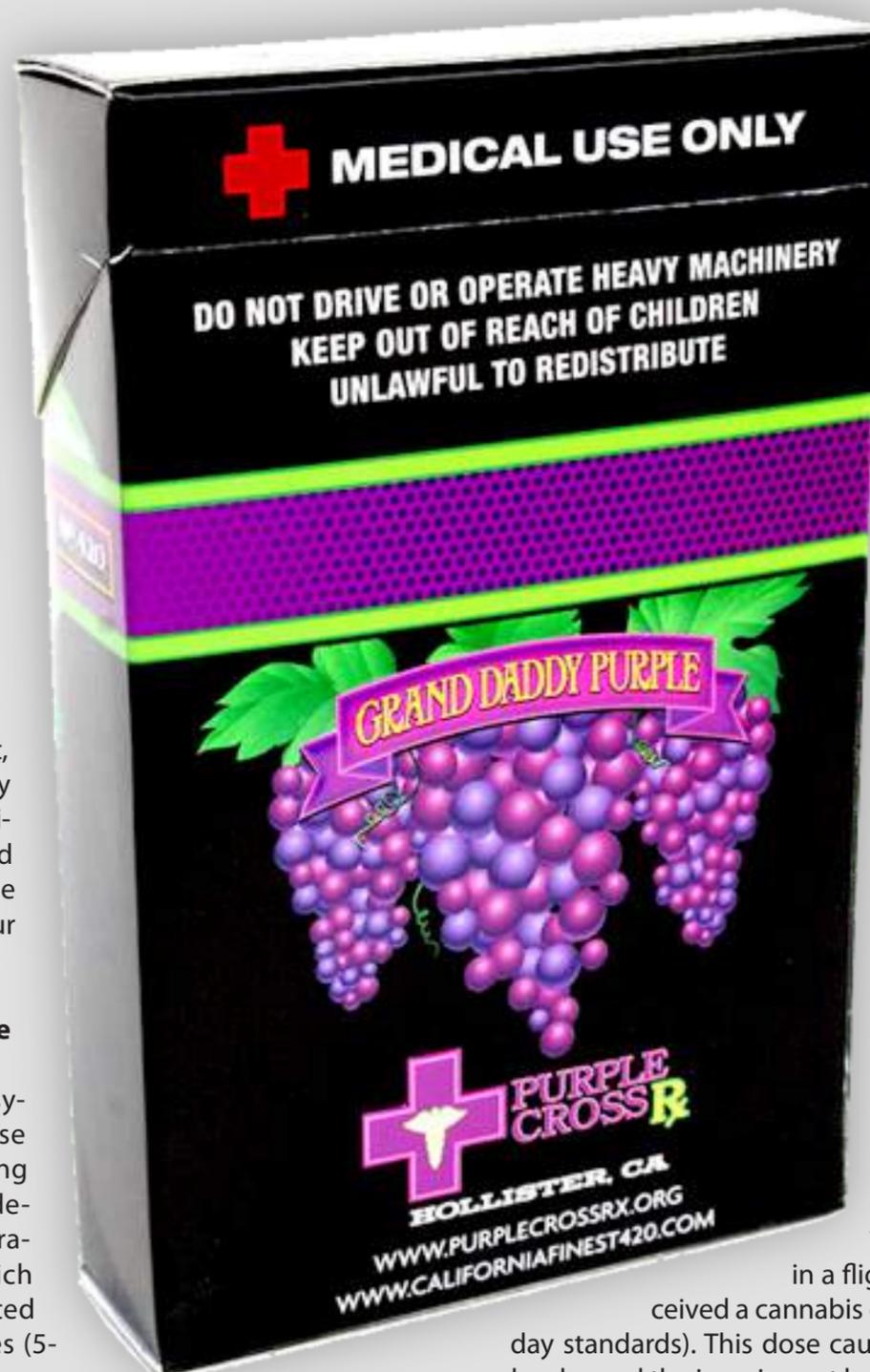
The main feature of the recreational use of cannabis is that it produces a euphoriant effect or 'high'. The high can be induced with doses of THC as low as 2.5 mg in a herbal cigarette and includes a feeling of intoxication, with decreased anxiety, alertness, depression and tension and increased sociability (if taken in friendly surroundings). The high comes on within minutes of smoking and then reaches a plateau lasting 2 hours or more, depending on dose. It is not surprising that the overwhelming reason for taking cannabis given by recreational users is simply 'pleasure' (Webb et al, 1996, 1998). However, cannabis can also produce dysphoric reactions, including severe anxiety and panic, paranoia and psychosis. These reactions are dose-related and more common in naïve users, anxious subjects and psychologically vulnerable individuals. (Psychiatric reactions including aggravation or precipitation of schizophrenia are described by Johns, 2001).

Effects on perception

Accompanying the high, and often contributing to it, cannabis produces perceptual changes. Colours may seem brighter, music more vivid, emotions more poignant and meaningful. Spatial perception is distorted and time perception is impaired so that perceived time goes faster than clock time. Hallucinations may occur with high doses.

Effects on cognition and psychomotor performance

Not surprisingly, cannabis impairs cognitive and psychomotor performance. The effects are similar to those of alcohol and benzodiazepines and include slowing of reaction time, motor incoordination, specific defects in short-term memory, difficulty in concentration and particular impairment in complex tasks which require divided attention. The effects are dose-related but can be demonstrated after relatively small doses (5-10 mg THC in a joint), even in experienced cannabis users, and have been shown in many studies across a wide range of neurocognitive and psychomotor tests. These effects are additive with those of other central nervous system depressants.



Driving and piloting skills

These effects combine to affect skills related to driving a vehicle or flying an aeroplane. Numerous studies have shown that cannabis impairs road-driving performance and have linked cannabis use with increased incidence of road traffic accidents. In the UK, USA, Australia, New Zealand and many European countries, cannabis is the most common drug, apart from alcohol, to be detected in drivers involved in fatal accidents or stopped for impaired driving. A large proportion of such drivers have not taken alcohol or have concentrations below the legal limit. For example, in two studies from the UK Department of Transport (Everest et al, 1989; Department of Environment, Transport and the Regions, 1998), no alcohol was detected post-mortem in 70% and 80%, respectively, in road traffic accident fatalities testing positive for cannabis. In Australia (Road Safety Committee, 1995) only half of surviving drivers of vehicle collisions involving death or life-threatening injuries who tested positive for cannabis had also taken alcohol. In Norway, 56% of a sample of drug-impaired drivers negative for alcohol gave positive blood samples for THC (Gjerde & Kinn, 1991). From the USA, McBay (1986) had earlier found that 75% of a sample of drivers with cannabinoids in their blood were also intoxicated with alcohol. The World Health Organization (1997, p. 15) concluded:

“There is sufficient consistency and coherence from experimental studies and studies of cannabinoid levels among accident victims...to conclude that there is an increased risk of motor vehicle accidents among persons who drive when intoxicated with cannabis....The risk is magnified when cannabis is combined with intoxicating doses of alcohol”

Piloting an aeroplane is an even more complex task than driving a car and cannabis has been shown in several investigations seriously to impair aircraft piloting skills. The results of one placebo-controlled study are shown in Fig. 4 (Leirer et al, 1991). The subjects were nine licensed pilots, highly trained in a flight simulator task, who were current cannabis users. They received a cannabis cigarette containing 20 mg THC (a moderate dose by present-day standards). This dose caused a significant decrement in performance compared with placebo and the impairment lasted over 24 hours after this single dose. Furthermore, most of the pilots were unaware that their performance was still impaired at 24 hours. Several pilots reported that they had actually flown while high on cannabis, and the authors noted that in at least one aeroplane crash the pilot was known to have taken cannabis some hours before

flying and to have made a similar landing misjudgement (poor alignment on the runway) as was noted in experimental studies.

There is evidence that similar long-lasting impairments apply to motor cyclists, train drivers, signal operators, air traffic controllers and operators of heavy machinery. However, a problem is that because of the very slow elimination of cannabinoids, there is no accurate way of relating blood, urine, saliva or sweat concentrations to the degree of intoxication of the driver or pilot at the time of an accident, no way of telling exactly when the last dose was taken and no proof that cannabis was actually the cause of an accident.

Long-term effects of chronic use

There is considerable evidence, reviewed by Hall et al (1994), that performance in heavy, chronic cannabis users remains impaired even when they are not actually intoxicated. These impairments, especially of attention, memory and ability to process complex information, can last for many weeks, months or even years after cessation of cannabis use (Solowij, 1998). Whether or not there is permanent cognitive impairment in heavy long-term users is not clear.

Tolerance, dependence, withdrawal effects

Tolerance has been shown to develop to many effects of cannabis including the high and many systemic effects, and a cannabis withdrawal syndrome has been clearly demonstrated in controlled studies in both animals and man (Jones, 1983; Kouri et al, 1999). The withdrawal syndrome has similarities to alcohol, opiate and benzodiazepine withdrawal states and includes restlessness, insomnia, anxiety, increased aggression, anorexia, muscle tremor and autonomic effects. A daily oral dose of 180 mg of THC (one or two modern, good-quality joints) for 11-21 days is sufficient to produce a well-defined withdrawal syndrome (Jones, 1983). The development of tolerance leads some cannabis users to escalate dosage, and the presence of withdrawal syndrome encourages continued drug use. Thus, chronic cannabis use can lead to drug dependence,



and reports from the USA, UK and New Zealand (Roffman & Barnhart, 1987; Stephens et al, 1993) indicate that many cannabis users are now seeking treatment for cannabis dependence.

Systemic effects Cardiovascular effects

Cannabinoids produce a dose-related tachycardia which may reach rates of up to 160 beats/minute or more, although tolerance develops with chronic use. There is also a widespread vasodilation and reddening of the conjunctivae, a characteristic sign of cannabis use (Paton & Pertwee, 1973). Postural hypotension and fainting may occur. These and other cardiovascular effects may carry a risk for individuals with preexisting cardiac disease, and several cases of acute and sometimes fatal cardiac incidents have been reported in young cannabis smokers.

Effects on the respiratory system

The smoke from herbal cannabis preparations contains all the same constituents (apart from nicotine) as tobacco smoke, including carbon monoxide, bronchial irritants, tumour initiators (mutagens), tumour promoters and carcinogens (British Medical Association, 1997). The tar from a cannabis cigarette contains higher concentrations of benzantracenes and benzpyrenes, both of which are carcinogens, than tobacco smoke. It has been estimated that smoking a cannabis cigarette results in approximately a five-fold greater increase in carboxyhaemoglobin concentration, a three-fold greater amount of tar inhaled and retention in the respiratory tract of one-third more tar than smoking a tobacco cigarette (Wu et al, 1988; Benson & Bentley, 1995). This is mainly due to the way a cannabis joint is smoked, with deep and prolonged inhalation and no filter. In addition, cannabis has a higher combustion temperature than tobacco.

Chronic cannabis smoking is associated with bronchitis and emphysema. It has been calculated that smoking 3-4 cannabis cigarettes a day is associated with the same evidence of acute and chronic bronchitis and the same degree of damage to the bronchial mucosa as 20 or more tobacco cigarettes a day (Benson & Bentley, 1995). Prospective studies of the long-term effects on the lungs of chronic cannabis smoking are lacking, but some authors suggest that chronic airways disease and bronchogenic carcinoma may be as great a risk as with tobacco smoking. In addition, there appears to be an increased incidence of rare forms of oropharyngeal cancer in young people who smoke cannabis chronically.

Effects on other systems

Cannabis also has immunosuppressant and endocrine effects although the clinical significance of these is still not clear. Chronic cannabis use appears to carry reproductive risks, both to the mother during pregnancy and childbirth and to the foetus and neonate, although these areas need further study. The full extent of long-term health risks of chronic cannabis use (if today's young smokers continue the habit) may require a latent period of 10-20 years to be revealed.



Introduction Source

The British Journal of Psychiatry • February 2001
Pharmacology and effects of cannabis: a brief review
By C. Heather Ashton

http://bjp.rcpsych.org/content/178/2/101?ijkey=d22c4cca66b8b243500a140776096919b8ca6c09&keytype2=tf_ipsecsha



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CANNABIS • 2016 PEER REVIEW

Cannabis: Effects in the Central Nervous System. Therapeutic, societal and legal consequences

Rivera-Olmos VM1, Parra-Bernal MC.

Departamento de Neurología, Baylor College of Medicine, Houston, Texas, EUA
vrivera@bcm.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27428345>

The consumption of marijuana extracted from *Cannabis sativa* and *indica* plants involves an important cultural impact in Mexico. Their psychological stimulatory effect is widely recognized; their biochemical and molecular components interact with CB1 and CB2 (endocannabinoid system) receptors in various central nervous system structures (CNS) and immune cells. The psychoactive element Δ -9-tetrahydrocannabinol (THC) can be reproduced synthetically. Systematic reviews show evidence of therapeutic effectiveness of therapeutic marijuana only for certain symptoms of multiple sclerosis (spasticity, spasms and pain), despite attempts for its widespread use, including refractory childhood epilepsy. Evidence indicates significant adverse effects of smoked marijuana on the structure, functioning and brain connectivity. Cannabis exposure during pregnancy affects fetal brain development, potentially leading to later behavioral problems in children. Neuropsychological tests and advanced imaging techniques show involvement in the learning process in adolescents with substance use. Also, marijuana increases the cognitive impairment in patients with multiple sclerosis. Social and ethical consequences to legally free marijuana for recreational use may be deleterious transcendentally. The medicinal or psychoactive cannabinol no addictive effect requires controlled proven efficacy and safety before regulatory approval studies.

Methods In Molecular Biology • September 2016

Need for Methods to Investigate Endocannabinoid Signaling

By M. Maccarrone

Department of Medicine, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128, Rome, Italy
European Center for Brain Research/Santa Lucia Foundation IRCCS, Via del Fosso di Fiorano 64, 00143, Rome, Italy
m.maccarrone@unicampus.it

<http://www.ncbi.nlm.nih.gov/pubmed/27245886>

Endocannabinoids (eCBs) are endogenous lipids able to activate cannabinoid receptors, the primary molecular targets of the cannabis (*Cannabis sativa*) active principle $\Delta(9)$ -tetrahydrocannabinol. During the last 20 years, several N-acylethanolamines and acylesters have been shown to act as eCBs, and a complex array of receptors, metabolic enzymes, and transporters (that altogether form the so-called eCB system) has been shown to finely tune their manifold biological activities. It appears now urgent to develop methods and protocols that allow to assay in a specific and quantitative manner the distinct components of the eCB system, and that can properly localize them within the cell. A brief overview of eCBs and of the proteins that bind, transport, and metabolize these lipids is presented here, in order to put in a better perspective the relevance of methodologies that help to disclose molecular details of eCB signaling in health and disease. Proper methodological approaches form also the basis for a more rationale and effective drug design and therapeutic strategy to combat human disorders.

Aberrant epilepsy-associated mutant Nav1.6 sodium channel activity can be targeted with cannabidiol

Patel RR1, Barbosa C2, Brustovetsky T2, Brustovetsky N3, Cummins TR4.

1. Program in Medical Neuroscience, Neuroscience Research Building, 320 West 15th St, Indianapolis, IN, 46202, USA
 2. Paul and Carole Stark Neurosciences Research Institute, 320 West 15th St, Indianapolis, IN, 46202, USA
 - 2,3. Department of Pharmacology and Toxicology, Indiana University School of Medicine, 635 Barnhill Drive, Indianapolis, IN, 46202, USA
 - 3,1. Program in Medical Neuroscience, Neuroscience Research Building, 320 West 15th St, Indianapolis, IN, 46202, USA
 2. Paul and Carole Stark Neurosciences Research Institute, 320 West 15th St, Indianapolis, IN, 46202, USA
 3. Department of Pharmacology and Toxicology, Indiana University School of Medicine, 635 Barnhill Drive, Indianapolis, IN, 46202, USA
 - 4,1. Program in Medical Neuroscience, Neuroscience Research Building, 320 West 15th St, Indianapolis, IN, 46202, USA
 2. Paul and Carole Stark Neurosciences Research Institute, 320 West 15th St, Indianapolis, IN, 46202, USA
 3. Department of Pharmacology and Toxicology, Indiana University School of Medicine, 635 Barnhill Drive, Indianapolis, IN, 46202, USA
- trcummin@iu.edu

<http://brain.oxfordjournals.org/content/139/8/2164.long>

Mutations in brain isoforms of voltage-gated sodium channels have been identified in patients with distinct epileptic phenotypes. Clinically, these patients often do not respond well to classic anti-epileptics and many remain refractory to treatment. Exogenous as well as endogenous cannabinoids have been shown to target voltage-gated sodium channels and cannabidiol has recently received attention for its potential efficacy in the treatment of childhood epilepsies. In this study, we further investigated the ability of cannabinoids to modulate sodium currents from wild-type and epilepsy-associated mutant voltage-gated sodium channels. We first determined the biophysical consequences of epilepsy-associated missense mutations in both Nav1.1 (arginine 1648 to histidine and asparagine 1788 to lysine) and Nav1.6 (asparagine 1768 to aspartic acid and leucine 1331 to valine) by obtaining whole-cell patch clamp recordings in human embryonic kidney 293T cells with 200 μ M Nav β 4 peptide in the pipette solution to induce resurgent sodium currents. Resurgent sodium current is an atypical near threshold current predicted to increase neuronal excitability and has been implicated in multiple disorders of excitability. We found that both mutations in Nav1.6 dramatically increased resurgent currents while mutations in Nav1.1 did not. We then examined the effects of anandamide and cannabidiol on peak transient and resurgent currents from wild-type and mutant channels. Interestingly, we found that cannabidiol can preferentially target resurgent sodium currents over peak transient currents generated by wild-type Nav1.6 as well as the aberrant resurgent and persistent current generated by Nav1.6 mutant channels. To further validate our findings, we examined the effects of cannabidiol on endogenous sodium currents from striatal neurons, and similarly we found an inhibition of resurgent and persistent current by cannabidiol. Moreover, current clamp recordings show that cannabidiol reduces overall action potential firing of striatal neurons. These findings suggest that cannabidiol could be exerting its anticonvulsant effects, at least in part, through its actions on voltage-gated sodium channels, and resurgent current may be a promising therapeutic target for the treatment of epilepsy syndromes.

Neural mechanisms of sensitivity to peer information in young adult cannabis users

Gilman JM^{1,2,3}, Schuster RM^{4,5}, Curran MT⁴, Calderon V⁴, van der Kouwe A^{6,5}, Evins AE^{4,5}.

1. Department of Psychiatry, Center for Addiction Medicine, Massachusetts General Hospital, Boston, MA, USA
 2. Department of Radiology, Athinoula A. Martinos Center in Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA
 3. Harvard Medical School, Boston, MA, USA
 4. Department of Psychiatry, Center for Addiction Medicine, Massachusetts General Hospital, Boston, MA, USA
 5. Harvard Medical School, Boston, MA, USA
 6. Department of Radiology, Athinoula A. Martinos Center in Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA
- jgilman1@partners.org

<http://www.ncbi.nlm.nih.gov/pubmed/27068178>

Though social influence is a critical factor in the initiation and maintenance of marijuana use, the neural correlates of influence in those who use marijuana are unknown. In this study, marijuana-using young adults (MJ; $n = 20$) and controls (CON; $n = 23$) performed a decision-making task in which they made a perceptual choice after viewing the choices of unknown peers via photographs, while they underwent functional magnetic resonance imaging scans. The MJ and CON groups did not show differences in the overall number of choices that agreed with versus opposed group influence, but only the MJ group showed reaction time slowing when deciding against group choices. Longer reaction times were associated with greater activation of frontal regions. The MJ group, compared to CON, showed significantly greater activation in the caudate when presented with peer information. Across groups, caudate activation was associated with self-reported susceptibility to influence. These findings indicate that young adults who use MJ may exhibit increased effort when confronted with opposing peer influence, as well as exhibit greater responsiveness of the caudate to social information. These results not only better define the neural basis of social decisions, but also suggest that marijuana use is associated with exaggerated neural activity during decision making that involves social information.

The Role of the Endocannabinoid System in the Brain-Gut Axis

Sharkey KA¹, Wiley JW².

1. Hotchkiss Brain Institute and Snyder Institute of Chronic Diseases, Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada
2. Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA
Electronic address: ksharkey@ucalgary.ca

<http://www.ncbi.nlm.nih.gov/pubmed/27133395>

The actions of cannabis are mediated by receptors that are part of an endogenous cannabinoid system. The endocannabinoid system (ECS) consists of the naturally occurring ligands N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), their biosynthetic and degradative enzymes, and the cannabinoid (CB) receptors CB1 and CB2. The ECS is a widely distributed transmitter system that controls gut functions peripherally and centrally. It is an important physiologic regulator of gastrointestinal motility. Polymorphisms in the gene encoding CB1 (CNR1) have been associated with some forms of irritable bowel syndrome. The ECS is involved in the control of nausea and vomiting and visceral sensation. The homeostatic role of the ECS also extends to the control of intestinal inflammation. We review the mechanisms by which the ECS links stress and visceral pain. CB1 in sensory ganglia controls visceral sensation, and transcription of CNR1 is modified through epigenetic processes under conditions of chronic stress. These processes might link stress with abdominal pain. The ECS is also involved centrally in the manifestation of stress, and endocannabinoid signaling reduces the activity of hypothalamic-pituitary-adrenal pathways via actions in specific brain regions, notably the prefrontal cortex, amygdala, and hypothalamus. Agents that modulate the ECS are in early stages of development for treatment of gastrointestinal diseases. Increasing our understanding of the ECS will greatly advance our knowledge of interactions between the brain and gut and could lead to new treatments for gastrointestinal disorders.

Cannabis use frequency and use-related impairment among African-American and White users: the impact of cannabis use motives

Buckner JD1, Shah SM1, Dean KE1, Zvolensky MJ2.

1. Department of Psychology, Louisiana State University, 236 Audubon Hall, Baton Rouge, LA 70803, USA

2. Department of Psychology, University of Houston & University of Texas MD Anderson Cancer Center, 126 Heyne Building, Houston, TX 77204, USA

Full text with 54 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752436/>

Cannabis use motives are differentially related to cannabis-related impairment and coping motives appear to have the strongest relation to use-related impairment. However, it is currently unknown whether African-American individuals differ from White persons in reasons for using cannabis. It is also unknown whether motives' relations to cannabis use and related impairment vary as a function of race. The present study examined the role of race on cannabis use motives and tested whether motives' relations with cannabis use and related impairment differed by race.

African-American participants did not significantly differ from White participants on cannabis use frequency or use-related impairment. African-American participants endorsed more social motives than White participants. Race interacted with social, coping, and conformity motives to predict cannabis-related impairment such that these motives were positively related to cannabis impairment among

Although African-American and White participants do not differ in their cannabis use frequency or cannabis-related impairment, they appear to use cannabis for different reasons. Further, conformity, coping, and social motives were differentially associated with cannabis-related impairment as a function of race. Findings suggest motives for cannabis use should be contextualised in the context of race.

Journal Of Alzheimers Disease • August 2016

Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study

Shelef A1, Barak Y1, Berger U2, Paleacu D1, Tadger S1, Plopsky I1, Baruch Y1.

1. Abarbanel Mental Health Center, Bat-Yam, Israel and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
2. Department of Psychology, Bar-Ilan University, Ramat-Gan, Israel

<http://www.ncbi.nlm.nih.gov/pubmed/26757043>

Tetrahydrocannabinol (THC) is a potential treatment for Alzheimer's disease (AD).

Eleven AD patients were recruited to an open label, 4 weeks, prospective trial. Ten patients completed the trial. Significant reduction in CGI severity score (6.5 to 5.7; $p < 0.01$) and NPI score were recorded (44.4 to 12.8; $p < 0.01$). NPI domains of significant decrease were: Delusions, agitation/aggression, irritability, apathy, sleep and caregiver distress.

Adding Medical Cannabis Oil to Alzheimer's patients' pharmacotherapy is safe and a promising treatment option.

Support Care Cancer • August 2016

Medical marijuana use in head and neck squamous cell carcinoma patients treated with radiotherapy

Elliott DA1, Nabavizadeh N2, Romer JL2, Chen Y3, Holland JM2.

1. Department of Radiation Medicine, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239, USA
2. Department of Radiation Medicine, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239, USA
3. Department of Public Health & Preventive Medicine, Oregon Health & Science University, Portland, OR, 97239, USA
elliotta@ohsu.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/27005465>

The purpose of the study was to better understand why patients with history of head and neck cancer (HNC) treated with radiotherapy are using medical marijuana (MM).

Most patients smoked marijuana (12 patients), while others reported ingestion (4 patients), vaporizing (3 patients), and use of homemade concentrated oil (1 patient). Six patients reported prior recreational marijuana use before diagnosis. MM provided benefit in altered sense, weight maintenance, depression, pain, appetite, dysphagia, xerostomia, muscle spasm, and sticky saliva. HNC patients report MM use to help with long-term side effects of radiotherapy.

Addiction • August 2016

Ecological momentary assessment of working memory under conditions of simultaneous marijuana and tobacco use

Schuster RM^{1,2}, Mermelstein RJ^{3,4}, Hedeker D⁵.

<http://www.ncbi.nlm.nih.gov/pubmed/26857917>

Relative to when individuals did not use these substances, working memory decreased with acute marijuana and alcohol use and increased with acute tobacco use. However, the putative effect of marijuana on working memory and the facilitative effect of tobacco on working memory were no longer present when used simultaneously with tobacco and alcohol, respectively. Data suggest that tobacco use may compensate for working memory decrements from marijuana among young adults and highlight the importance of investigating further the negative impact of alcohol use on cognition.

Investigation of a recently detected 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol isomer: Studies on the degradation of 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol glucuronide

Hanisch S1, Paulke A1, Toennes SW2.

1. Institute of Legal Medicine, University of Frankfurt, Kennedyallee 104, D-60596, Frankfurt/Main, Germany
Electronic address: toennes@em.uni-frankfurt.de

<http://www.ncbi.nlm.nih.gov/pubmed/274483>

An isomer of the tetrahydrocannabinol (THC) metabolite 11-nor-9-carboxy- Δ 9-THC (THCCOOH) had been detected in blood of cannabis users. The present study was initiated to elucidate whether the labile metabolite THCCOOH-glucuronide could be the precursor. THCCOOH-glucuronide was incubated in human serum and albumin (HSA) solution at various temperatures (-18, 4.5, 22 and 37°C) and pH values (pH 7.4 and 8.3) for seven days in the presence or absence of the esterase inhibitor sodium fluoride. Analysis of incubation samples was performed using LC-MS/MS. Marked degradation of THCCOOH-glucuronide was observed at 37°C. It was found that not only THCCOOH, but also the isomer is a degradation product of THCCOOH-glucuronide and its in-vivo production is assumed. Degradation to THCCOOH and the isomer occurred at alkaline pH, in the presence of fluoride-sensitive esterases and of HSA alone. To inhibit isomer formation during sample storage, refrigeration and controlling of the pH are recommended. However, THCCOOH and the isomer exhibit similar properties during incubations in serum, but differ in their interaction with HSA. The present study confirmed the nature of the isomer as degradation product of the abundant THC metabolite THCCOOH-glucuronide. Serum albumin and esterases are obviously involved. **The isomer is formed not only during storage, but also under physiological conditions, suggesting that it can be considered an in-vivo metabolite. However, the chemical structure of the isomer remains unknown and further research is necessary.**

Analytical And Bioanalytical Chemistry • July 2016

Simultaneous quantification of 11 cannabinoids and metabolites in human urine by liquid chromatography tandem mass spectrometry using WAX-S tips

Andersson M1, Scheidweiler KB2, Sempio C1, Barnes AJ1, Huestis MA1,3.

<http://www.ncbi.nlm.nih.gov/pubmed/27422645>

We developed and validated a comprehensive, simple, and rapid LC-MS/MS cannabinoid urine method for quantification of 11 cannabinoids and metabolites. This method is being used in a controlled cannabis administration study, investigating urine cannabinoid markers documenting recent cannabis use, chronic frequent smoking, or route of drug administration and potentially improving urine cannabinoid result interpretation.

Psychopharmacology • July 2016

Subjective aggression during alcohol and cannabis intoxication before and after aggression exposure

De Sousa Fernandes Perna EB1, Theunissen EL2, Kuypers KP2, Toennes SW3, Ramaekers JG2.

1,2. Department Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, P.O. Box 616, 6200 MD, Maastricht, The Netherlands

3. Department of Forensic Toxicology, Institute of Legal Medicine, Goethe University of Frankfurt, Frankfurt, Germany
e.desousafernandes@maastrichtuniversity.nl

<http://www.ncbi.nlm.nih.gov/pubmed/27422568>

Alcohol and cannabis use have been implicated in aggression. Alcohol consumption is known to facilitate aggression, whereas a causal link between cannabis and aggression has not been clearly demonstrated.

It is concluded that alcohol facilitates feelings of aggression whereas cannabis diminishes aggressive feelings in heavy alcohol and regular cannabis users, respectively.

Long-term hippocampal glutamate synapse and astrocyte dysfunctions underlying the altered phenotype induced by adolescent THC treatment in male rats

Zamberletti E1, Gabaglio M2, Grilli M3, Prini P2, Catanese A2, Pittaluga A4, Marchi M4, Rubino T2, Parolaro D5.

1. Dept. of Biotechnology and Life Sciences (DBSV), University of Insubria, Busto Arsizio, VA, Italy; Zardi Gori Foundation, Milan, Italy
 2. Dept. of Biotechnology and Life Sciences (DBSV), University of Insubria, Busto Arsizio, VA, Italy
 3. Department of Pharmacy (DiFAR), Pharmacology and Toxicology Section, University of Genoa, Genoa, Italy
 4. Department of Pharmacy (DiFAR), Pharmacology and Toxicology Section, University of Genoa, Genoa, Italy and Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy
 5. Dept. of Biotechnology and Life Sciences (DBSV), University of Insubria, Busto Arsizio, VA, Italy and Zardi Gori Foundation, Milan, Italy
- Electronic address: daniela.parolaro@uninsubria.it

<http://www.ncbi.nlm.nih.gov/pubmed/27422357>

Cannabis use has been frequently associated with sex-dependent effects on brain and behavior. We previously demonstrated that adult female rats exposed to delta-9-tetrahydrocannabinol (THC) during adolescence develop long-term alterations in cognitive performances and emotional reactivity, whereas preliminary evidence suggests the presence of a different phenotype in male rats. To thoroughly depict the behavioral phenotype induced by adolescent THC exposure in male rats, we treated adolescent animals with increasing doses of THC twice a day (PND 35-45) and, at adulthood, we performed a battery of behavioral tests to measure affective- and psychotic-like symptoms as well as cognition.

Poorer memory performance and psychotic-like behaviors were present after adolescent THC treatment in male rats, without alterations in the emotional component. At cellular level, the expression of the NMDA receptor subunit, GluN2B, as well as the levels of the AMPA subunits, GluA1 and GluA2, were significantly increased in hippocampal post-synaptic fractions from THC-exposed rats compared to controls. Furthermore, increases in the levels of the pre-synaptic marker, synaptophysin, and the post-synaptic marker, PSD95,

were also present. Interestingly, KCl-induced [³H]D-ASP release from hippocampal synaptosomes, but not gliosomes, was significantly enhanced in THC-treated rats compared to controls.

Moreover, in the same brain region, adolescent THC treatment also resulted in a persistent neuroinflammatory state, characterized by increased expression of the astrocyte marker, GFAP, increased levels of the pro-inflammatory markers, TNF- α , iNOS and COX-2, as well as a concomitant reduction of the anti-inflammatory cytokine, IL-10. Notably, none of these alterations was observed in the prefrontal cortex (PFC).

Together with our previous findings in females, these data suggest that the sex-dependent detrimental effects induced by adolescent THC exposure on adult behavior may rely on its ability to trigger different region-dependent changes in glutamate synapse and glial cells. **The phenotype observed in males is mainly associated with marked dysregulations in the hippocampus, whereas the prevalence of alterations in the emotional sphere in females is associated with profound changes in the prefrontal cortex.**

Psychopharmacology • July 2016

Effect of combined oral doses of Δ^9 -tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models

Rock EM1, Connolly C1, Limebeer CL1, Parker LA2,3.

1,2. Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, ON, N1G 2W1, Canada

3. Department of Psychology, University of Guelph, Guelph, ON, N1G 2W1, Canada

parkerl@uoguelph.ca

<http://www.ncbi.nlm.nih.gov/pubmed/27438607>

The purpose of this study was to evaluate the potential of oral combined cannabis constituents to reduce nausea.

Oral administration of subthreshold doses of THC and CBDA may be an effective new treatment for acute nausea and anticipatory nausea and appetite enhancement in chemotherapy patients.

Cannabinoids, inflammation, and fibrosis

Zurier RB1, Burstein SH2.

1,2. Department of Medicine University of Massachusetts Medical School, Worcester, Massachusetts
and Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts USA
robert.zurier@umassmed.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/27435265>

Cannabinoids apparently act on inflammation through mechanisms different from those of agents such as nonsteroidal anti-inflammatory drugs (NSAIDs). As a class, the cannabinoids are generally free from the adverse effects associated with NSAIDs. Their clinical development thus provides a new approach to treatment of diseases characterized by acute and chronic inflammation and fibrosis. A concise survey of the anti-inflammatory actions of the phytocannabinoids Δ 9-tetrahydrocannabinol (THC), cannabidiol, cannabichromene, and cannabinol is presented.

Mention is also made of the noncannabinoid plant components and pyrolysis products, followed by a discussion of 3 synthetic preparations-Cesamet (nabilone; Meda Pharmaceuticals, Somerset, NJ, USA), Marinol (THC; AbbVie, Inc., North Chicago, IL, USA), and Sativex (Cannabis extract; GW Pharmaceuticals, Cambridge United Kingdom)-that have anti-inflammatory effects.

A fourth synthetic cannabinoid, ajulemic acid (CT-3, AJA; Resunab; Corbus Pharmaceuticals, Norwood, MA, USA), is discussed in greater detail because it represents the most recent advance in this area and is currently undergoing 3 phase 2 clinical trials by Corbus Pharmaceuticals. The endogenous cannabinoids, including the closely related lipoamino acids, are then discussed.

The review concludes with a presentation of a possible mechanism for the anti-inflammatory and antifibrotic actions of these substances. Thus, several cannabinoids may be considered candidates for development as anti-inflammatory and antifibrotic agents. Of special interest is their possible use for treatment of chronic inflammation, a major unmet medical need.

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Small Molecule Detection in Saliva Facilitates Portable Tests of Marijuana Abuse

Lee JR1, Choi J2, Shultz TO1, Wang SX1,2.

1. Department of Materials Science and Engineering, Stanford University, Stanford, California 94305, USA

2. Department of Electrical Engineering, Stanford University, Stanford, California 94305, USA

<http://www.ncbi.nlm.nih.gov/pubmed/27434697>

As medical and recreational use of cannabis, or marijuana, becomes more prevalent, law enforcement needs a tool to evaluate whether drivers are operating vehicles under the influence of cannabis, specifically the psychoactive substance, tetrahydrocannabinol (THC). However, the cutoff concentration of THC that causes impairment is still controversial, and current on-site screening tools are not sensitive enough to detect trace amounts of THC in oral fluids. Here we present a novel sensing platform that employs giant magnetoresistive (GMR) biosensors integrated with a portable reader system and smartphone to detect THC in saliva using competitive assays. With a simple saliva collection scheme, we have optimized the assay to measure THC in the range from 0 to 50 ng/mL, covering most cutoff values proposed in previous studies. This work facilitates on-site screening for THC and shows potential for testing of other small molecule drugs and analytes in point-of-care (POC) settings.

Alterations in taste perception due to recreational drug use are due to smoking a substance rather than ingesting it

Dovey TM1, Boyland EJ2, Trayner P2, Miller J2, Rarmoul-Bouhadjar A3, Cole J2, Halford JC2.

1,3. Institute of Environment, Health & Societies, Department of Life Sciences, Marie Jahoda Building, Brunel University London, Uxbridge, UB8 3PH, United Kingdom

2. Department of Psychological Sciences, University of Liverpool, Eleanor Rathbone Building, Bedford Street South, Liverpool, L69 7ZA, United Kingdom

Electronic address: terence.dovey@brunel.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/27426619>

Two studies explored the differences in tastant (salt, sour, bitter, sweet and spicy) concentration preference between recreational drug users and abstainers. In study 1, 250 opportunistically recruited abstainers, cannabis only users and multiple-drug users completed psychometric questionnaires and a concentration preference tastant test. In study 2, 76 participants purposefully recruited abstainers, daily tobacco users, recreational cannabis users and daily cannabis users completed the same protocol as study 1. Study 1 demonstrated that both multiple drug users and cannabis users had a higher preference for salt and sour tastants than abstainers. Study 2 showed that daily cannabis and tobacco users had a higher preference for sweet and spicy tastants than recreational cannabis users and abstainers. As predicted, recreational drug users scored higher on both sensation-seeking and impulsivity compared to abstainers. Participants who habitually smoke tobacco or cannabis daily have different concentration preference for specific tastants. The data offered in this paper indicate that variation in recruitment strategy, definition of 'drug users', and mode of drug delivery, as well as multiple drug use, may explain the preference for stronger tastants in habitual drug users. Future research exploring the psychobiological underpinnings of the impact of drug use on food preferences should carefully define recreational drug user groups.

The therapeutic potential of the phytocannabinoid cannabidiol for Alzheimer's disease

Karl T1, Garner B, Cheng D.

1. School of Medicine, Western Sydney University, Campbelltown bNeuroscience Research Australia (NeuRA), Randwick cIllawarra Health and Medical Research Institute dSchool of Biological Sciences, University of Wollongong, Wollongong eVictor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia

<http://www.ncbi.nlm.nih.gov/pubmed/27471947>

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive loss of cognition. Over 35 million individuals currently have AD worldwide. Unfortunately, current therapies are limited to very modest symptomatic relief. The brains of AD patients are characterized by the deposition of amyloid- β and hyperphosphorylated forms of tau protein. AD brains also show neurodegeneration and high levels of oxidative stress and inflammation. The phytocannabinoid cannabidiol (CBD) possesses neuroprotective, antioxidant and anti-inflammatory properties and reduces amyloid- β production and tau hyperphosphorylation in vitro. CBD has also been shown to be effective in vivo making the phytocannabinoid an interesting candidate for novel therapeutic interventions in AD, especially as it lacks psychoactive or cognition-impairing properties. CBD treatment would be in line with preventative, multimodal drug strategies targeting a combination of pathological symptoms, which might be ideal for AD therapy. Thus, this review will present a brief introduction to AD biology and current treatment options before outlining comprehensively CBD biology and pharmacology, followed by in-vitro and in-vivo evidence for the therapeutic potential of CBD. We will also discuss the role of the endocannabinoid system in AD before commenting on the potential future of CBD for AD therapy.

Cannabis Use Surveillance By Sweat Analysis

Gambelunghe C1, Fucci N, Aroni K, Bacci M, Marcelli A, Rossi R.

1. Department of Surgical and Biomedical Science, Forensic Medicine, Forensic Science and Sports Medicine Section, University of Perugia, Piazza Luigi Severi 1, 06132 Sant'Andrea delle Fratte, Perugia, Italy
2. Public Health Institute, Legal Medicine Section, Sacred Heart Catholic University, Largo Francesco Vito, 1, 00168 Rome, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/27465974>

Sweat testing, an alternative matrix for establishing drug abuse, offers additional benefits to the more common biological samples. The authors developed a procedure using gas chromatography-mass spectrometry to test for Δ 9-tetrahydrocannabinol, 11-nor- Δ 9-tetrahydrocannabinol-9-carboxylic acid, cannabinol and cannabidiol in a sweat patch. The results were compared with urine and hair sample results.

Urine, hair, and sweat samples were simultaneously collected from 12 patients who were involved, respectively, in forensic case and monitoring abuse. Selectivity, linearity, limit of detection, limit of quantification, recovery, intra- and inter-day imprecision, and inaccuracy of the quantification procedure were validated. Limits of detection in hair were 0.05 ng/mg for Δ 9-tetrahydrocannabinol, cannabinol, cannabidiol and 0.005 ng/mg for 11-nor- Δ 9-tetrahydrocannabinol-9-carboxylic acid. The limit of detection for sweat was 0.30 ng/patch for all substances. The limit of quantification in hair was 0.1 ng/mg for Δ 9-tetrahydrocannabinol, cannabinol, cannabidiol and 0.01 ng/mg for 11-nor- Δ 9-tetrahydrocannabinol-9-carboxylic acid. The limit of quantification was 0.4 ng/patch in sweat for each analyte. Cannabinoid in urine was determined by means of immunochemical screening (cutoff 11-nor- Δ -tetrahydrocannabinol-9-carboxylic acid 50 ng/ml). All subjects tested positive for 11-nor- Δ 9-tetrahydrocannabinol-9-carboxylic acid and Δ 9-tetrahydrocannabinol in urine and hair. In sweat samples, Δ 9-tetrahydrocannabinol was found in all patches (0.4-2.0 ng/patch); six cases were positive for cannabinol (0.4-0.5 ng/patch) and three for cannabidiol (0.4-0.6 ng/patch); 11-nor- Δ 9-tetrahydrocannabinol-9-carboxylic acid was never detected in patches.

Present sweat analysis results integrated the information from hair and urine and showed that sweat analysis is a suitable, non-invasive method for monitoring compliance with rehabilitation therapy and for detecting recent cumulative use of cannabinoids.

Effects of Cannabidiol and Hypothermia on Short-Term Brain Damage in New-Born Piglets after Acute Hypoxia-Ischemia

Lafuente H1, Pazos MR2, Alvarez A3, Mohammed N2, Santos M2, Arizti M1, Alvarez FJ1, Martinez-Orgado JA4.

1. Neonatology Research Group, Biocruces Health Research Institute Bizkaia, Spain
2. Group of Cannabinoids Research on Neonatal Pathologies, Research Institute Puerta de Hierro Majadahonda Madrid, Spain
3. Department of Cell Biology, University of the Basque Country Leioa, Spain
4. Group of Cannabinoids Research on Neonatal Pathologies, Research Institute Puerta de Hierro Majadahonda Madrid, Spain
Department of Neonatology, Hospital Clínico San Carlos-Instituto de Investigación Sanitaria San Carlos (IdISSC) Madrid, Spain

Full text with 34 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4940392/>

Hypothermia is a standard treatment for neonatal encephalopathy, but nearly 50% of treated infants have adverse outcomes. Pharmacological therapies can act through complementary mechanisms with hypothermia improving neuroprotection. Cannabidiol could be a good candidate. Our aim was to test whether immediate treatment with cannabidiol and hypothermia act through complementary brain pathways in hypoxic-ischemic newborn piglets. Hypoxic-ischemic animals were randomly divided into four groups receiving 30 min after the insult: (1) normothermia and vehicle administration; (2) normothermia and cannabidiol administration; (3) hypothermia and vehicle administration; and (4) hypothermia and cannabidiol administration. Six hours after treatment, brains were processed to quantify the number of damaged neurons by Nissl staining. Proton nuclear magnetic resonance spectra were obtained and analyzed for lactate, N-acetyl-aspartate and glutamate. Metabolite ratios were calculated to assess neuronal damage (lactate/N-acetyl-aspartate) and excitotoxicity (glutamate/Nacetyl-aspartate). Western blot studies were performed to quantify protein nitrosylation (oxidative stress), content of caspase-3 (apoptosis) and TNF α (inflammation). Individually, the hypothermia and the cannabidiol treatments reduced the glutamate/Nacetyl-aspartate ratio, as well as TNF α and oxidized protein levels in newborn piglets subjected to hypoxic-ischemic insult. Also, both therapies reduced the number of necrotic neurons and prevented an increase in lactate/N-acetyl-aspartate ratio. The combined effect of hypothermia and cannabidiol on excitotoxicity, inflammation and oxidative stress, and on cell damage, was greater than either hypothermia or cannabidiol alone. The present study demonstrated that cannabidiol and hypothermia act complementarily and show additive effects on the main factors leading to hypoxic-ischemic brain damage if applied shortly after the insult.

Protective effect of cannabidiol on hydrogen peroxide-induced apoptosis, inflammation and oxidative stress in nucleus pulposus cells

Chen J1, Hou C2, Chen X1, Wang D1, Yang P1, He X1, Zhou J3, Li H1.

1. Department of Orthopaedic Surgery, Second Affiliated Hospital of Medical School of Xi'an Jiaotong University, Xi'an, Shaanxi 710004, P.R. China

2. Department of Geriatric Neurology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710068, P.R. China

3. Department of Orthopedics, Hong Hui Hospital, Xi'an Jiatong University College of Medicine, Xi'an, Shaanxi 710004, P.R. China

<http://www.ncbi.nlm.nih.gov/pubmed/?term=27430346>

Cannabidiol, a major component of marijuana, protects nerves, and exerts antispasmodic, anti-inflammatory and anti-anxiety effects. In the current study, the protective effect of cannabidiol was observed to prevent hydrogen peroxide (H₂O₂)-induced apoptosis, inflammation and oxidative stress in nucleus pulposus cells. Nucleus pulposus cells were isolated from rats and cultured in vitro, and H₂O₂ was used to construct the nucleus pulposus cell model. Cell viability of the nucleus pulposus cells was assessed using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. The ratio of apoptotic cells, and caspase-3 or cyclooxygenase-2 (COX-2) mRNA expression was analyzed by annexin V-fluorescein isothiocyanate/propidium-iodide staining and reverse transcription-quantitative polymerase chain reaction, respectively. The quantities of interleukin (IL)-1 β and interleukin-6 were measured using a series of assay kits. B-cell lymphoma 2 (Bcl-2) and inducible nitric oxide synthase (iNOS) protein expression levels were analyzed using western blotting. The present study identified that cannabidiol enhanced cell viability and reduced apoptosis in H₂O₂-treated nucleus pulposus cells in vitro using a lumbar disc herniation (LDH) model. In addition, cannabidiol reduced caspase-3 gene expression and augmented the Bcl-2 protein expression levels in the nucleus pulposus cells following H₂O₂ exposure. Pre-treatment with cannabidiol suppressed the promotion of COX-2, iNOS, IL-1 β and IL-6 expression in the nucleus pulposus cells following H₂O₂ exposure. Taken together, these results suggest that cannabidiol potentially exerts its protective effect on LDH via the suppression of anti-apoptosis, anti-inflammation and anti-oxidative activities in nucleus pulposus cells.

Abnormal cannabidiol attenuates experimental colitis in mice, promotes wound healing and inhibits neutrophil recruitment

Krohn RM1, Parsons SA2, Fichna J3, Patel KD2, Yates RM4, Sharkey KA5, Storr MA6.

1. Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, AB Canada
Snyder Institute for Chronic Diseases, University of Calgary, Calgary, AB Canada
2. Snyder Institute for Chronic Diseases, University of Calgary, Calgary, AB Canada
Department of Physiology and Pharmacology, University of Calgary, Calgary, AB Canada
3. Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, AB Canada
Snyder Institute for Chronic Diseases, University of Calgary, Calgary, AB Canada
Department of Biochemistry, Medical University of Lodz, Lodz, Poland
4. Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, AB Canada
Department of Comparative Biology and Experimental Medicine, Faculty of Veterinary Medicine, University of Calgary, Calgary, AB Canada
5. Snyder Institute for Chronic Diseases, University of Calgary, Calgary, AB Canada
Department of Physiology and Pharmacology, University of Calgary, Calgary, AB Canada
Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB Canada
6. Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, AB Canada
Snyder Institute for Chronic Diseases, University of Calgary, Calgary, AB Canada
Division of Gastroenterology, Department of Medicine, Ludwig Maximilians University of Munich, Marchioninistrasse 15, 81377 Munich, Germany

Full text with 50 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944257/>

Non-psychotropic atypical cannabinoids have therapeutic potential in a variety of inflammatory conditions including those of the gastrointestinal tract. Here we examined the effects of the atypical cannabinoid abnormal cannabidiol (Abn-CBD) on wound healing, inflammatory cell recruitment and colitis in mice. Colitis was induced in CD1 mice by a single intrarectal administration of trinitrobenzene sulfonic acid (TNBS, 4 mg/100 μ l in 30 % ethanol) and Abn-CBD and/or the antagonists O-1918 (Abd-CBD), AM251 (CB1 receptor) and AM630 (CB2 receptor), were administered intraperitoneally (all 5 mg/kg, twice daily for 3 days). The degree of colitis was assessed macro- and microscopically and tissue myeloperoxidase activity was determined. The effects of Abn-CBD on wound healing of endothelial and epithelial cells (LoVo) were assessed in a scratch injury assay. Human neutrophils were employed in Transwell assays or perfused over human umbilical vein endothelial cells (HUVEC) to study the effect of Abn-CBD on neutrophil accumulation and transmigration. TNBS-induced colitis was attenuated by treatment with Abn-CBD. Histological, macroscopic colitis scores and tissue myeloperoxidase activity were significantly reduced. These effects were inhibited by O-1918, but not by AM630, and only in part by AM251. Wound healing of both HUVEC and LoVo cells was enhanced by Abn-CBD. Abn-CBD inhibited neutrophil migration towards IL-8, and dose-dependently inhibited accumulation of neutrophils on HUVEC.

Abn-CBD is protective against TNBS-induced colitis, promotes wound healing of endothelial and epithelial cells and inhibits neutrophil accumulation on HUVEC monolayers. Thus, the atypical cannabinoid Abn-CBD represents a novel potential therapeutic in the treatment of intestinal inflammatory diseases.

Storage and disposal of medical cannabis among patients with cancer: Assessing the risk of diversion and unintentional digestion

Sznitman SR1, Goldberg V2, Sheinman-Yuffe H2, Flechter E2, Bar-Sela G2,3.

1. Department of Health Promotion, School of Public Health, University of Haifa, Haifa, Israel

2. Division of Oncology, Rambam Health Care Campus, Haifa, Israel

3. Integrated Oncology and Palliative Care Unit, Rambam Health Care Campus, Technion-Israel Institute of Technology, Haifa, Israel

<http://www.ncbi.nlm.nih.gov/pubmed/27420392>

Increasingly more jurisdictions worldwide are legalizing medical cannabis. The current study investigated the risk of medical cannabis diversion and unintentional digestion among oncology patients treated with medical cannabis and caregivers of recently deceased patients who were treated with medical cannabis.

A total of 123 oncology patients treated with medical cannabis and 37 caregivers of deceased oncology patients treated with medical cannabis were interviewed regarding practices and the information received concerning the safe storage and disposal of medical cannabis, as well as experiences of theft, diversion, and unintentional digestion.

High rates of suboptimal storage were reported and caregivers were found to be particularly unlikely to have received information regarding the safe storage and disposal of medical cannabis. Few incidences of theft, diversion, and unintentional digestion were reported.

Oncologists and other health care providers have an important, yet unfilled, role to play with regard to educating patients and caregivers of the importance of the safe storage and disposal of medical cannabis. Interventions designed to alert patients treated with medical cannabis and their caregivers to the problem of diversion, along with strategies to limit it, have the potential to limit diversion and unintentional exposure to medical cannabis.

Fluorinated Cannabidiol Derivatives: Enhancement of Activity in Mice Models Predictive of Anxiolytic, Antidepressant and Antipsychotic Effects

Breuer A1, Haj CG1, Fogaça MV2, Gomes FV2, Silva NR2, Pedrazzi JF3, Del Bel EA4, Hallak JC3, Crippa JA3, Zuardi AW3, Mechoulam R1, Guimarães FS2.

1. Institute for Drug Research, Medical Faculty, Hebrew University, Jerusalem, Israel

2. Departments of Pharmacology, Medical School of Ribeirão Preto, University of São Paulo, São Paulo, Brazil

3. Neuroscience and Behavior, Medical School of Ribeirão Preto, University of São Paulo, São Paulo, Brazil

4. Department of Morphology, Physiology and Pathology, School of Odontology of Ribeirão Preto, University of São Paulo, São Paulo, Brazil

<http://www.ncbi.nlm.nih.gov/pubmed/27416026>

Cannabidiol (CBD) is a major *Cannabis sativa* constituent, which does not cause the typical marijuana psychoactivity. However, it has been shown to be active in a numerous pharmacological assays, including mice tests for anxiety, obsessive-compulsive disorder, depression and schizophrenia. In human trials the doses of CBD needed to achieve effects in anxiety and schizophrenia are high. We report now the synthesis of 3 fluorinated CBD derivatives, one of which, 4'-F-CBD (HUF-101) (1), is considerably more potent than CBD in behavioral assays in mice predictive of anxiolytic, antidepressant, antipsychotic and anti-compulsive activity. Similar to CBD, the anti-compulsive effects of HUF-101 depend on cannabinoid receptors.

Cannabinoids for Symptom Management and Cancer Therapy: The Evidence

By M. P. Davis

From Cleveland Clinic Lerner School of Medicine, Case Western University, and Palliative Medicine and Supportive Oncology Services
Division of Solid Tumor, Taussig Cancer Institute, The Cleveland Clinic, Cleveland, Ohio

<http://www.ncbi.nlm.nih.gov/pubmed/27407130>

Structurally, there are 3 groups of cannabinoids. Multiple studies, most of which are of moderate to low quality, demonstrate that tetrahydrocannabinol (THC) and oromucosal cannabinoid combinations of THC and cannabidiol (CBD) modestly reduce cancer pain.

Dronabinol and nabilone are better antiemetics for chemotherapy-induced nausea and vomiting (CINV) than certain neuroleptics, but are not better than serotonin receptor antagonists in reducing delayed emesis, and cannabinoids have largely been superseded by neurokinin-1 receptor antagonists and olanzapine; both cannabinoids have been recommended for breakthrough nausea and vomiting among other antiemetics.

Multiple cancers express cannabinoid receptors directly related to the degree of anaplasia and grade of tumor. Preclinical in vitro and in vivo studies suggest that cannabinoids may have anticancer activity.

Paradoxically, cannabinoid receptor antagonists also have antitumor activity. There are few randomized smoked or vaporized cannabis trials in cancer on which to judge the benefits of these forms of cannabinoids on symptoms and the clinical course of cancer. Smoked cannabis has been found to contain Aspergillosis. Immunosuppressed patients should be advised of the risks of using “medical marijuana” in this regard.

Aspergillosis

Aspergillosis is the name given to a wide variety of diseases caused by infection by fungi of the genus *Aspergillus*. The majority of cases occur in people with underlying illnesses such as tuberculosis or chronic obstructive pulmonary disease (COPD), but with otherwise healthy immune systems. People with deficient immune systems such as patients undergoing stem cell transplantation, chemotherapy or patients with AIDS are at risk of more disseminated disease. Acute invasive Aspergillosis occurs when the immune system fails to prevent *Aspergillus* spores from entering the bloodstream via the lungs. Without the body mounting an effective immune response, fungal cells are free to disseminate throughout the body and can infect major organs such as the heart and kidneys.

A content analysis of tweets about high-potency marijuana

Cavazos-Rehg PA1, Sowles SJ2, Krauss MJ2, Agbonavbare V2, Gruzca R2, Bierut L2.

1,2. Department of Psychiatry, Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO, 63110, USA
Electronic address: rehgp@psychiatry.wustl.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27402550>

“Dabbing” involves heating extremely concentrated forms of marijuana to high temperatures and inhaling the resulting vapor. We studied themes describing the consequences of using highly concentrated marijuana by examining the dabbing-related content on Twitter.

Tweets containing dabbing-related keywords were collected from 1/1-1/31/2015 (n=206,854). A random sample of 5000 tweets was coded for content according to pre-determined categories about dabbing-related behaviors and effects experienced using a crowdsourcing service. An examination of tweets from the full sample about respiratory effects and passing out was then conducted by selecting tweets with relevant keywords.

Among the 5000 randomly sampled tweets, 3540 (71%) were related to dabbing marijuana concentrates. The most common themes included mentioning current use of concentrates (n=849; 24%), the intense high and/or extreme effects from dabbing (n=763; 22%) and excessive/heavy dabbing (n=517; 15%). Extreme effects included both physiological (n=124/333; 37%) and psychological effects (n=55/333; 17%). The most common physiologic effects, passing out (n=46/333; 14%) and respiratory effects (n=30/333; 9%), were then further studied in the full sample of tweets. Coughing was the most common respiratory effect mentioned (n=807/1179; 68%), and tweeters commonly expressed dabbing with intentions to pass out (416/915; 45%).

This study adds to the limited understanding of marijuana concentrates and highlights self-reported physical and psychological effects from this type of marijuana use. Future research should further examine these effects and the potential severity of health consequences associated with concentrates.

Therapeutic approach to pain in neurodegenerative diseases: current evidence and perspectives

de Tommaso M1, Kunz M2, Valeriani M3.

1. Neurophysiopathology of Pain Section, SMBNOS Department, Bari Aldo Moro University, Bari, Italy
2. Department of General Practice, Section Gerontology, University Medical Center Groningen, Groningen, The Netherlands
3. Division of Neurology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/27400329>

Neurodegenerative diseases are increasing in parallel to the lengthening of survival. The management of Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD-related disorders, and motor neuron diseases (MND), is mainly targeted to motor and cognitive impairment, with special care for vital functions such as breathing and feeding.

The present review focuses on chronic pain in main neurodegenerative diseases, addressing current evidence on pain therapeutic management, pain frequency and clinical features, and possible pathophysiological mechanisms. The search on PubMed had no time limits and was performed by searching for the following key issues: pain, dementia, Alzheimer disease, Parkinson's disease, extrapyramidal disorders, motoneuronal disease, Amyotrophic lateral sclerosis, FXTAS, frequency, pathophysiology, treatments, therapy, efficacy, opioids, side effects. No controlled therapeutic trials and guidelines are currently available. The effects of current therapies such as L-Dopa or riluzole on pain symptoms are not clear.

Emerging evidences on the possible anti-nociceptive effects of cannabis or botulinum toxin might be available soon.

Expert commentary: Pain needs to be better evaluated and fully considered in the global management of neurodegenerative disease because a more focused treatment may have a positive impact on the global burden of these devastating disorders.

The endocannabinoid system - a target for the treatment of LUTS?

Hedlund P1, Gratzke C2.

1. Division of Drug Research, Department of Medical and Health Sciences, Linköping University, 581 83 Linköping, Sweden
2. Department of Urology, Ludwig-Maximilians-University Munich, Marchioninistrasse 15, 81377 Munich, Germany

<http://www.ncbi.nlm.nih.gov/pubmed/27377161>

Lower urinary tract symptoms (LUTS) are common in all age groups and both sexes, resulting in tremendous personal suffering and a substantial burden to society. Antimuscarinic drugs are the mainstay of symptom management in patients with LUTS, although their clinical utility is limited by the high prevalence of adverse effects, which often limit patients' long-term adherence to these agents.

Data from controversial studies in the 1990s revealed the positive effects of marijuana-based compounds on LUTS, and sparked an interest in the possibility of treating bladder disorders with cannabis. Increased understanding of cannabinoid receptor pharmacology and the discovery of endogenous ligands of these receptors has prompted debate and further research into the clinical utility of exogenous cannabinoid receptor agonists relative to the unwanted psychotropic effects of these agents.

Currently, the endocannabinoid system is considered as a potential drug target for pharmacological management of LUTS, with a more favourable adverse event profile than antimuscarinic agents.

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Transient Retinal Dysfunctions after Acute Cannabis Use

Schwitzer T1, Robert MP, Giersch A, Angioi-Duprez K, Ingster-Moati I, Pon-Monnier A, Schwan R, Laprevote V.

EA 7298, INGRES, Universitx00E9; de Lorraine, Vandx0153;uvre-lx00E8;s-Nancy, France

<http://www.ncbi.nlm.nih.gov/pubmed/27376753>

Although cannabis is very widespread worldwide, the impact of cannabis on visual function remains poorly understood. Here, we report the first documented case of neuroretinal dysfunction after acute cannabis smoking. This observation was favored by the need of an annual ophthalmic evaluation in the context of a chloroquine intake for a systemic lupus erythematosus in a 47-year-old heavy cannabis user. A complete ophthalmic evaluation including visual acuity tests, intraocular pressure, fundoscopic examination, automated 10° central visual field, full-field electroretinogram (ERG) and multifocal ERG was performed twice - 30 min and 5 h after cannabis smoking. A strong decrease (up to 48%) in the a-wave amplitude of the full-field ERG was measured 30 min after cannabis smoking for all scotopic responses compared with the responses 5 h after smoking. Other tests showed reproducible results between the 2 series of measurements. This clinical case suggests that acute inhalation of cannabis affects the photoreceptors functioning. This rare situation suggests further investigations are required on the impact of cannabis on retinal processing, especially since cannabis has been incriminated in car injuries.

International Maritime Health • July 2016

Prevalence of cannabis and cocaine consumption in French fishermen in South Atlantic region in 2012-2013 and its policy consequences

Fort E1, Lassiège T, Bergeret A.

Univ Lyon, Université Claude Bernard Lyon 1, Ifsttar, UMRESTTE UMR T-9405, F- 69373, Lyon, France
emmanuel.fort@univ-lyon1.fr

Full text PDF

https://journals.viamedica.pl/international_maritime_health/article/view/47178

The aim of the study was to evaluate the use of cannabis and cocaine among fishermen followed in occupational medicine in the ports of Aquitaine and Charente-Maritime (Direction interrégionale de la mer Sud-Atlantique [DIRM-SA]).

About 20% of fishermen were former smokers. A third of the fishermen are at risk for excessive drinking according to the AUDIT-C. The prevalence of cannabis experimentation was estimated at 58%. The prevalence of positive urine test for cannabis was 28%. The prevalence of experimentation with cocaine was about 16%. The prevalence of positive urine test for cocaine was 4.5%.

In accordance with its objectives, this study allows objectifying cannabis and cocaine consumption among fishermen. The national rules for fitness at sea have to be modified by introducing the use of urinary tests by occupational physician.

“Those edibles hit hard”: Exploration of Twitter data on cannabis edibles in the U.S.

Lamy FR1, Daniulaityte R2, Sheth A3, Nahhas RW4, Martins SS5, Boyer EW6, Carlson RG2.

1. Center for Interventions, Treatment, and Addictions Research (CITAR), Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Suite 124, Dayton, OH 45420-4006, USA
Ohio Center of Excellence in Knowledge-enabled Computing (Kno.e.sis), Department of Computer Science and Engineering, Wright State University, Dayton, OH, USA
2. Center for Interventions, Treatment, and Addictions Research (CITAR), Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Suite 124, Dayton, OH 45420-4006, USA
3. Ohio Center of Excellence in Knowledge-enabled Computing (Kno.e.sis), Department of Computer Science and Engineering, Wright State University, Dayton, OH, USA
4. Center for Global Health, Department of Community Health, Wright State University Boonshoft School of Medicine, Dayton, OH, United States
Department of Psychiatry, Wright State University Boonshoft School of Medicine, Dayton, OH, USA
5. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA
6. Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Electronic address: francois.lamy@wright.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27185160>

Several states in the U.S. have legalized cannabis for recreational or medical uses. In this context, cannabis edibles have drawn considerable attention after adverse effects were reported. This paper investigates Twitter users' perceptions concerning edibles and evaluates the association edibles-related tweeting activity and local cannabis legislation.

Tweets were collected between May 1 and July 31, 2015, using Twitter API and filtered through the eDrugTrends/Twitris platform. A random sample of geolocated tweets was manually coded to evaluate Twitter users' perceptions regarding edibles. Raw state proportions of Twitter users mentioning edibles were adjusted relative to the total number of Twitter users per state. Differences in adjusted proportions of Twitter users mentioning edibles between states with different cannabis legislation status were assessed via a permutation test.

We collected 100,182 tweets mentioning cannabis edibles with 26.9% (n=26,975) containing state-level geolocation. Adjusted percentages of geolocated Twitter users posting about edibles were significantly greater in states that allow recreational and/or medical use of cannabis. The differences were statistically significant. Overall, cannabis edibles were generally positively perceived among Twitter users despite some negative tweets expressing the unreliability of edible consumption linked to variability in effect intensity and duration.

Our findings suggest that Twitter data analysis is an important tool for epidemiological monitoring of emerging drug use practices and trends. Results tend to indicate greater tweeting activity about cannabis edibles in states where medical THC and/or recreational use are legal. Although the majority of tweets conveyed positive attitudes about cannabis edibles, analysis of experiences expressed in negative tweets confirms the potential adverse effects of edibles and calls for educating edibles-naïve users, improving edibles labeling, and testing their THC content.

Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis

Hammell DC1, Zhang LP2, Ma F2, Abshire SM2, McIlwrath SL2, Stinchcomb AL1, Westlund KN2.

Full text with 68 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4851925/>

Current arthritis treatments often have side-effects attributable to active compounds as well as route of administration. Cannabidiol (CBD) attenuates inflammation and pain without side-effects, but CBD is hydrophobic and has poor oral bio-availability. Topical drug application avoids gastrointestinal administration, first pass metabolism, providing more constant plasma levels.

This study examined efficacy of transdermal CBD for reduction in inflammation and pain, assessing any adverse effects in a rat complete Freund's adjuvant-induced monoarthritic knee joint model. CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction. Joint circumference and immune cell invasion in histological sections were measured to indicate level of inflammation. Paw withdrawal latency (PWL) in response to noxious heat stimulation determined nociceptive sensitization, and exploratory behaviour ascertained animal's activity level. Measurement of plasma CBD concentration provided by transdermal absorption revealed linearity with 0.6-6.2 mg/day doses. Transdermal CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. PWL recovered to near baseline level. Immunohistochemical analysis of spinal cord (CGRP, OX42) and dorsal root ganglia (TNF α) revealed dose-dependent reductions of pro-inflammatory biomarkers. Results showed 6.2 and 62 mg/day were effective doses. Exploratory behaviour was not altered by CBD indicating limited effect on higher brain function.

These data indicate that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviours and inflammation without evident side-effects.

Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity

Reece AS1, Hulse GK2.

1,2. School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA 6009, Australia
Electronic address: sreece@bigpond.net.au

<http://www.ncbi.nlm.nih.gov/pubmed/27208973>

The recent demonstration that massive scale chromosomal shattering or pulverization can occur abruptly due to errors induced by interference with the microtubule machinery of the mitotic spindle followed by haphazard chromosomal annealing, together with sophisticated insights from epigenetics, provide profound mechanistic insights into some of the most perplexing classical observations of addiction medicine, including cancerogenesis, the younger and aggressive onset of addiction-related cancerogenesis, the heritability of addictive neurocircuitry and cancers, and foetal malformations.

Tetrahydrocannabinol (THC) and other addictive agents have been shown to inhibit tubulin polymerization which perturbs the formation and function of the microtubules of the mitotic spindle.

This disruption of the mitotic machinery perturbs proper chromosomal segregation during anaphase and causes micronucleus formation which is the primary locus and cause of the chromosomal pulverization of chromothripsis and downstream genotoxic events including oncogene induction and tumour suppressor silencing.

Moreover the complementation of multiple positive cannabis-cancer epidemiological studies, and replicated dose-response relationships with established mechanisms fulfils causal criteria. This information is also consistent with data showing acceleration of the aging process by drugs of addiction including alcohol, tobacco, cannabis, stimulants and opioids.

THC shows a non-linear sigmoidal dose-response relationship in multiple pertinent in vitro and preclinical genotoxicity assays, and in this respect is similar to the serious major human mutagen thalidomide. Rising community exposure, tissue storage of cannabinoids, and increasingly potent phytocannabinoid sources, suggests that the threshold mutagenic dose for cancerogenesis will increasingly be crossed beyond the developing world, and raise transgenerational transmission of teratogenicity as an increasing concern.

Trends In Pharmacology Science • July 2016

Beyond Cannabis: Plants and the Endocannabinoid System

By E.B. Russo

PHYTECS, 1875 Century Park East, Suite 2250, Los Angeles CA 90067, USA
Electronic address: ethanrusso@comcast.net

<http://www.ncbi.nlm.nih.gov/pubmed/27179600>

Plants have been the predominant source of medicines throughout the vast majority of human history, and remain so today outside of industrialized societies. One of the most versatile in terms of its phytochemistry is cannabis, whose investigation has led directly to the discovery of a unique and widespread homeostatic physiological regulator, the endocannabinoid system. While it had been the conventional wisdom until recently that only cannabis harbored active agents affecting the endocannabinoid system, in recent decades the search has widened and identified numerous additional plants whose components stimulate, antagonize, or modulate different aspects of this system. These include common foodstuffs, herbs, spices, and more exotic ingredients: kava, chocolate, black pepper, and many others that are examined in this review.

Pharmacokinetics of Cannabis in Cancer Cachexia-Anorexia Syndrome

Reuter SE^{1,2,3}, Martin JH⁴.

1. School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia

2. Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia

3,4. Department of Clinical Pharmacology, University of Newcastle, Calvary Mater Newcastle Hospital (Level 5), Waratah, 2298, NSW, Australia
jen.martin@newcastle.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/26883879>

Anorexia can affect up to 90% of people with advanced cancer. It is a complex symptom associated with changes in taste, lack of hunger at meal-times and lack of food enjoyment. Associated weight loss is part of the physical decline that occurs as cancer worsens. Weight loss can also occur from cachexia, the increased metabolism of energy due to raised inflammatory cytokines, liver metastases and other factors seen in several advanced cancers. Independent of anorexia, although frequently associated (where it is referred to as the cachexia-anorexia syndrome), it accounts for a significant amount of morbidity and deaths in people with cancer. In particular, quality of life for the patient and the family is significantly affected with this syndrome as it causes anxiety and distress. Therefore, it is important that research into therapies is undertaken, particularly focusing on an understanding of the pharmacokinetic properties of compounds in this cachexic population. Cannabinoids are one such group of therapies that have received a large amount of media focus recently. However, there appears to be a lack on rigorous pharmacokinetic data of these complex and varied compounds in the cachexic population. Similarly, there is a lack of pharmacokinetic data in any population group for the non- tetrahydrocannabinol (THC) and cannabidiol (CBD) cannabinoids (often due to the lack of analytical standards for quantification). This review will thus examine the pharmacokinetics of major cannabinoids i.e. THC and CBD in a cancer population.

Overall, based on the current literature, evidence for the use of cannabinoids for the treatment of cancer-related cachexia-anorexia syndrome remains equivocal. A high-quality, rigorous, phase I/II study to elicit pharmacokinetic dose-concentration and concentration-response data, with a clinically acceptable mode of delivery to reduce inpatient variability and enable more consistent bioavailability is needed in this population.

Endocannabinoid system as a regulator of tumor cell malignancy - biological pathways and clinical significance

Pysznik M1, Tabarkiewicz J2, Łuszczki JJ3.

1. Centre for Innovative Research in Medical and Natural Sciences, Faculty of Medicine; Department of Immunology, Faculty of Medicine, University of Rzeszów, Rzeszów Postgraduate School of Molecular Medicine, Medical University of Warsaw, Warszawa
2. Centre for Innovative Research in Medical and Natural Sciences, Faculty of Medicine; Department of Immunology, Faculty of Medicine, University of Rzeszów, Rzeszów
3. Department of Pathophysiology, Medical University of Lublin; Isobolographic Analysis Laboratory, Institute of Agricultural Medicine, Lublin, Poland

<http://www.ncbi.nlm.nih.gov/pubmed/27486335>

The endocannabinoid system (ECS) comprises cannabinoid receptors (CBs), endogenous cannabinoids, and enzymes responsible for their synthesis, transport, and degradation of (endo)cannabinoids. To date, two CBs, CB1 and CB2, have been characterized; however, orphan G-protein-coupled receptor GPR55 has been suggested to be the third putative CB. Several different types of cancer present abnormal expression of CBs, as well as other components of ECS, and this has been shown to correlate with the clinical outcome. Although most effects of (endo)cannabinoids are mediated through stimulation of classical CBs, they also interact with several molecules, either pro-survival or pro-apoptotic molecules. It should be noted that the mode of action of exogenous cannabinoids differs significantly from that of endocannabinoid and results from the studies on their activity both in vivo and in vitro could not be easily compared. This review highlights the main signaling pathways involved in the antitumor activity of cannabinoids and the influence of their activation on cancer cell biology. We also discuss changes in the expression pattern of the ECS in various cancer types that have an impact on disease progression and patient survival. A growing amount of experimental data imply possible exploitation of cannabinoids in cancer therapy.

Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis

Hammell DC1, Zhang LP2, Ma F2, Abshire SM2, McIlwrath SL2, Stinchcomb AL1, Westlund KN2.

1. Department of Pharmaceutical Sciences, University of Kentucky College of Pharmacy, Lexington, KY, 40536-0082, USA

2. Department of Physiology, University of Kentucky College of Medicine, Lexington, KY, 40536-0298, USA

Full text with 68 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4851925/>

Current arthritis treatments often have side-effects attributable to active compounds as well as route of administration. Cannabidiol (CBD) attenuates inflammation and pain without side-effects, but CBD is hydrophobic and has poor oral bioavailability. Topical drug application avoids gastrointestinal administration, first pass metabolism, providing more constant plasma levels.

This study examined efficacy of transdermal CBD for reduction in inflammation and pain, assessing any adverse effects in a rat complete Freund's adjuvant-induced monoarthritic knee joint model. CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction. Joint circumference and immune cell invasion in histological sections were measured to indicate level of inflammation. Paw withdrawal latency (PWL) in response to noxious heat stimulation determined nociceptive sensitization, and exploratory behaviour ascertained animal's activity level. Measurement of plasma CBD concentration provided by transdermal absorption revealed linearity with 0.6-6.2 mg/day doses. Transdermal CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. PWL recovered to near baseline level. Immunohistochemical analysis of spinal cord (CGRP, OX42) and dorsal root ganglia (TNF α) revealed dose-dependent reductions of pro-inflammatory biomarkers. Results showed 6.2 and 62 mg/day were effective doses. Exploratory behaviour was not altered by CBD indicating limited effect on higher brain function.

These data indicate that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviours and inflammation without evident side-effects.

Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents

Fasinu PS1, Phillips S1, ElSohly MA1,2, Walker LA1,3.

1. The National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, MS
2. Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, University, MS
3. Department of BioMolecular Sciences, School of Pharmacy, The University of Mississippi, University, MS

<http://www.ncbi.nlm.nih.gov/pubmed/?term=27285147>

States and the federal government are under growing pressure to legalize the use of cannabis products for medical purposes in the United States. Sixteen states have legalized (or decriminalized possession of) products high in cannabidiol (CBD) and with restricted $\Delta(9)$ -tetrahydrocannabinol ($\Delta(9)$ -THC) content. In most of these states, the intent is for use in refractory epileptic seizures in children, but in a few states, the indications are broader. This review provides an overview of the pharmacology and toxicology of CBD; summarizes some of the regulatory, safety, and cultural issues relevant to the further exploitation of its antiepileptic or other pharmacologic activities; and assesses the current status and prospects for clinical development of CBD and CBD-rich preparations for medical use in the United States. Unlike $\Delta(9)$ -THC, CBD elicits its pharmacologic effects without exerting any significant intrinsic activity on the cannabinoid receptors, whose activation results in the psychotropic effects characteristic of $\Delta(9)$ -THC, and CBD possesses several pharmacologic activities that give it a high potential for therapeutic use. CBD exhibits neuroprotective, antiepileptic, anxiolytic, antipsychotic, and antiinflammatory properties. In combination with $\Delta(9)$ -THC, CBD has received regulatory approvals in several European countries and is currently under study in trials registered by the U.S. Food and Drug Administration in the United States. A number of states have passed legislation to allow for the use of CBD-rich, limited $\Delta(9)$ -THC-content preparations of cannabis for certain pathologic conditions. CBD is currently being studied in several clinical trials and is at different stages of clinical development for various medical indications. Judging from clinical findings reported so far, CBD and CBD-enriched preparations have great potential utility, but uncertainties regarding sourcing, long-term safety, abuse potential, and regulatory dilemmas remain.

Colorado Cannabis Legalization and Its Effect on Emergency Care

Kim HS1, Monte AA2.

1. Denver Health Residency in Emergency Medicine, Denver Health Hospital and Authority, Denver, CO, and the Center for Education in Health Sciences and Department of Emergency Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL
2. Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, and Rocky Mountain Poison and Drug Center, Denver, CO.
Electronic address: howard.kim@northwestern.edu

Full text with 27 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4939797/>

Colorado legalized the use of medical marijuana in 2000, although it was not truly commercialized in the state until the US attorney general ceased the prosecution of marijuana users and suppliers in 2009. The result was striking: from January 2009 to January 2011, the number of registered medical marijuana licenses in Colorado increased from 5,051 to 118,895.

In 2012, Colorado voted to legalize recreational marijuana beginning in 2014, making it the first state alongside Washington to permit recreational use. Several other states have recently legalized the use of medical or recreational marijuana, with other states considering similar measures (see map next page). Given this trend, emergency physicians in

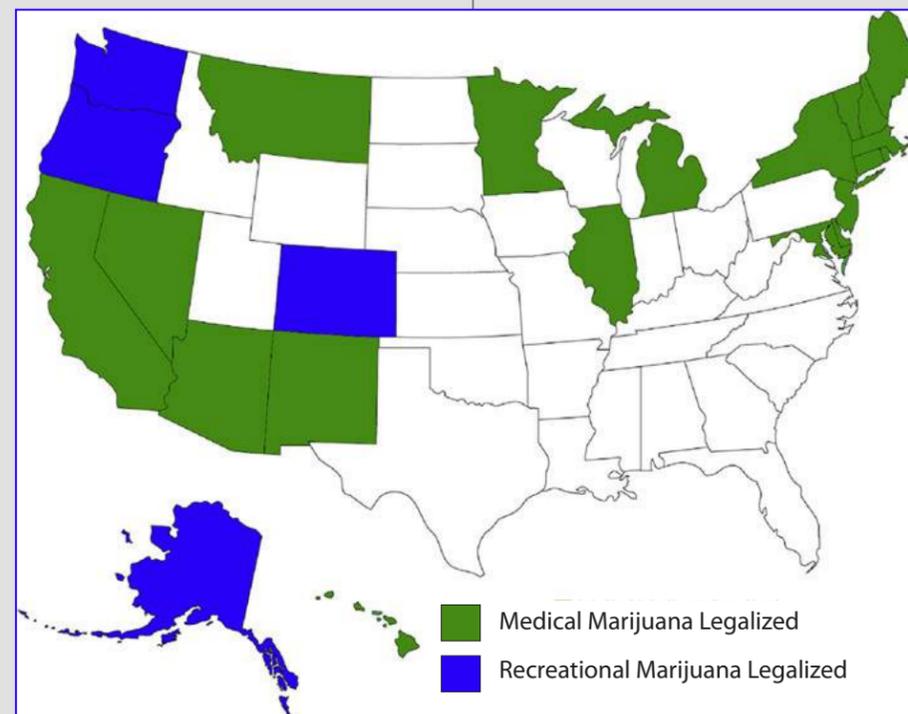
training will likely be confronted with increasing volumes of marijuana-related emergency department (ED) visits and may learn from Colorado's recent experience with increased availability of marijuana products.

The Colorado experience with medical and recreational marijuana legalization suggests several trends that are likely to become increasingly prevalent in the future practice of current emergency medicine residents as more states pursue legalization. It is clear that marijuana availability and use in Colorado significantly increased after the commercialization of medical marijuana. Providers in states with impending legalization measures should become familiar with the symptoms and management of acute marijuana intoxication, as

well as understand the effects on chronic diseases frequently observed in the ED. A systematic review of the public health implications of retail marijuana legalization performed by the Colorado Department of Public Health can be accessed online.³

Emergency physicians should be particularly aware of the unique characteristics of edible marijuana products, which can result in severe symptoms in novice users or children. Additionally, ED providers should be aware of an increasing number of motor vehicle drivers under the influence of marijuana.²² Although it is not clear that marijuana is responsible for increased rates of motor vehicle crashes, concomitant marijuana use can diminish clinical sobriety and cloud physical examination, particularly in regard to cervical spine clearance. This review does not address the therapeutic benefits of

medical marijuana, because doing so would recapitulate an abundance of existing literature. ED providers should be prepared, however, to address an increasing frequency of questions from patients that are based on references from popular culture, such as the use of marijuana for seizure disorder,²³ chronic pain, and substitution for opioid therapy,^{24–26} as well as adverse health effects of long-term marijuana use.²⁷ Most important, emergency physicians in training should understand that a larger proportion of ED patients will be using marijuana products and engage their patients in open discussion of the risks and benefits of use. It is apparent that emergency physicians in training will thus need to achieve a broader knowledge of marijuana-related issues than previous generations of emergency physicians, and to this end, residency program directors should make an effort to integrate this topic into their residency curriculums.



Cognitive behavioral therapy program for cannabis use cessation in first-episode psychosis patients: study protocol for a randomized controlled trial

González-Ortega I1,2,3, Echeburúa E4,5, García-Alocén A6, Vega P4,6, González-Pinto A4,6,7.

1. Center for Biomedical Research in the Mental Health Network (CIBERSAM), Madrid, Spain
2. Department of Psychiatry, Araba University Hospital, Olaguibel Street 29, 01004, Vitoria, Spain
3. School of Psychology, University of the Basque Country, San Sebastián, Spain
4. Center for Biomedical Research in the Mental Health Network (CIBERSAM), Madrid, Spain
5. School of Psychology, University of the Basque Country, San Sebastián, Spain
6. Department of Psychiatry, Araba University Hospital, Olaguibel Street 29, 01004, Vitoria, Spain
7. School of Medicine, University of the Basque Country, Vitoria, Spain
itxaso.gonzalezortega@osakidetza.eus

Full text with 62 references

<http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1507-x>

The high rate of cannabis use among patients with first-episode psychosis (FEP), as well as the associated negative impact on illness course and treatment outcomes, underlines the need for effective interventions in these populations. However, to date, there have been few clinical treatment trials (of pharmacological or psychological interventions) that have specifically focused on addressing comorbid cannabis use among these patients. The aim of this paper is to describe the design of a study protocol for a randomized controlled trial in which the objective is to assess the efficacy of a specific cognitive behavioral therapy program for cannabis cessation in patients with FEP compared to standard treatment (psychoeducation).

This study provides the description of a clinical trial design based on specific cognitive behavioral therapy for cannabis cessation in FEP patients, aiming to improve clinical and functional outcome, as well as tackling the addictive disorder.

Early marijuana initiation: The link between prenatal marijuana exposure, early childhood behavior, and negative adult roles

Goldschmidt L1, Richardson GA2, Larkby C2, Day NL2.

1. Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA

2. Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

Electronic address: lidush@pitt.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27263091>

We investigated the associations among gestational factors including prenatal marijuana exposure (PME), child behavior at age 3, early age of onset of marijuana use (EAOM, <15years), and adult roles at 22years. Participants were drawn from the Maternal Health Practices and Child Development (MHPCD) Project, a longitudinal study of prenatal substance exposure in offspring who have been studied for over 22years since the prenatal phase. Data from the prenatal, birth, 3-, and 22-year phases (N=608) were used in the present study. Age of onset of offspring substance use was determined based on data from the 14-, 16-, and 22-year phases. The subjects were of lower socioeconomic status, 43% were Caucasian and the remaining were African-American, and 48% were males. Early childhood behavior was significantly ($p<0.05$) related to EAOM after controlling for PME, birth and childhood environmental risk factors, and Conduct Disorder. EAOM was significantly associated with negative adult roles including increased risk of being arrested ($p<0.001$), lower educational attainment ($p<0.001$), having a child without being married ($p<0.05$), and unemployment at 22years ($p<0.001$). The correlations between PME and negative adult roles and between early childhood behavior and negative adult roles were also statistically significant. Pathway analysis demonstrated that EAOM significantly mediated the associations between PME and fulfillment of adult roles and between early childhood behavior and adult roles. There are a number of intervention points that could be targeted that would have a long-term impact on lowering the probability of EAOM and less success in adult roles.

Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood

Sagar KA1,2, Dahlgren MK1,3, Racine MT1, Dreman MW1, Olson DP1,2, Gruber SA1,2.

1. Cognitive and Clinical Neuroimaging Core, McLean Imaging Center, McLean Hospital, Belmont, Massachusetts, USA

2. Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA

3. Department of Psychology, Tufts University, Medford, Massachusetts, USA

Full text with 74 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4898690/>

Marijuana is the most widely used illicit substance in those diagnosed with bipolar I disorder. However, there is conflicting evidence as to whether marijuana may alleviate or exacerbate mood symptomatology. As bipolar disorder and marijuana use are individually associated with cognitive impairment, it also remains unclear whether there is an additive effect on cognition when bipolar patients use marijuana. The current study aimed to determine the impact of marijuana on mood in bipolar patients and to examine whether marijuana confers an additional negative impact on cognitive function. Twelve patients with bipolar disorder who smoke marijuana (MJBP), 18 bipolar patients who do not smoke (BP), 23 marijuana smokers without other Axis 1 pathology (MJ), and 21 healthy controls (HC) completed a neuropsychological battery. Further, using ecological momentary assessment, participants rated their mood three times daily as well as after each instance of marijuana use over a four-week period. Results revealed that although the MJ, BP, and MJBP groups each exhibited some degree of cognitive impairment relative to HCs, no significant differences between the BP and MJBP groups were apparent, providing no evidence of an additive negative impact of BPD and MJ use on cognition. Additionally, ecological momentary assessment analyses indicated alleviation of mood symptoms in the MJBP group after marijuana use; MJBP participants experienced a substantial decrease in a composite measure of mood symptoms. Findings suggest that for some bipolar patients, marijuana may result in partial alleviation of clinical symptoms. Moreover, this improvement is not at the expense of additional cognitive impairment.

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Cannabis Use in Adolescence and Young Adulthood: A Review of Findings from the Victorian Adolescent Health Cohort Study

Coffey C1, Patton GC2.

1,2. Centre for Adolescent Health, Murdoch Childrens Research Institute, Royal Children's Hospital, University of Melbourne, Parkville, Victoria, Australia
george.patton@rch.org.au

<http://www.ncbi.nlm.nih.gov/pubmed/27254840>

The Victorian Adolescent Health Cohort Study (VAHCS) is a long-term Australian cohort study that has documented cannabis use in young Australians from the mid-teens to the mid-30s. The study findings have described the natural history of early cannabis use, remission, and escalation and the social and mental health consequences of different patterns of use. The adverse consequences of cannabis use are most clear-cut in heavy early adolescent users. These consequences include educational failure, persisting mental health problems, and progression to other substance use. For later onset and occasional users, the risks are lower and appear to entail modest elevations in risk for other drug use compared with never users. With growing evidence of health consequences, there is a strong case for actions around early heavy adolescent users. Prevention of early use, identification and treatment of early heavy users, and harm reduction through diversion of early heavy users away from the custodial justice system into health care are all priority responses.

Cannabis consumption patterns among frequent consumers in Uruguay

Boidi MF1, Queirolo R2, Cruz JM3.

1. Insights Research & Consulting, Canelones, Uruguay

Electronic address: fboidi@insightsresearchandconsulting.com

2. Department of Social and Political Sciences, Universidad Católica del Uruguay, Montevideo, Uruguay

3. Kimberly Green Latin American and Caribbean Center, Florida International University, Miami, FL, USA

<http://www.ncbi.nlm.nih.gov/pubmed/27397717>

In 2013, Uruguay became the first country to fully regulate the cannabis market, which now operates under state control. Cannabis can be legally acquired in three ways: growing it for personal use (self-cultivation), cannabis club membership, and from pharmacies (not yet implemented). Users must be entered into a confidential official registry to gain access.

This article presents findings of a Respondent Driven Sample survey of 294 high-frequency cannabis consumers in the Montevideo metropolitan area.

Frequent consumers resort to more than one method for acquiring cannabis, with illegal means still predominating after 1 year of the new regulation law. Cannabis users overwhelmingly support the current regulation, but many of them are reluctant to register.

Some of the attitudes and behaviors of the high-frequency consumers pose a challenge to the success of the cannabis law. Individuals relying on more than one method of access defy the single access clause, a prerequisite for legal use, while the maximum amount of cannabis individuals can access monthly seems too high even for most frequent consumers, which might promote the emergence of a grey market. Reluctance to register among a significant proportion of high-frequency consumers raises doubts about the law's ability to achieve its stated objectives.

What Can Rats Tell Us about Adolescent Cannabis Exposure? Insights from Preclinical Research

Renard J1, Rushlow WJ2, Laviolette SR2.

1. Addiction Research Group, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario
Department of Anatomy and Cell Biology, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario
2. Addiction Research Group, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario
Department of Anatomy and Cell Biology, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario
Department of Psychiatry, The Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario
jrenard@uwo.ca

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Marijuana is the most widely used drug of abuse among adolescents. Adolescence is a vulnerable period for brain development, during which time various neurotransmitter systems such as the glutamatergic, GABAergic, dopaminergic, and endocannabinoid systems undergo extensive reorganization to support the maturation of the central nervous system (CNS). Δ^9 -tetrahydrocannabinol (THC), the psychoactive component of marijuana, acts as a partial agonist of CB1 cannabinoid receptors (CB1Rs). CB1Rs are abundant in the CNS and are central components of the neurodevelopmental changes that occur during adolescence. Thus, overactivation of CB1Rs by cannabinoid exposure during adolescence has the ability to dramatically alter brain maturation, leading to persistent and enduring changes in adult cerebral function. Increasing preclinical evidence lends support to clinical evidence suggesting that chronic adolescent marijuana exposure may be associated with a higher risk for neuropsychiatric diseases, including schizophrenia. In this review, we present a broad overview of current neurobiological evidence regarding the long-term consequences of adolescent cannabinoid exposure on adult neuropsychiatric-like disorders.

In the weeds: a baseline view of cannabis use among legalizing states and their neighbours

Pacula RL1, Jacobson M2, Maksabedian EJ3.

1. Drug Policy Research Center, RAND, California, CA, USA
2. University of California, Irvine - Business School, Irvine, CA, USA
3. RAND, Pardee RAND Graduate School, Santa Monica, California, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26687431>

To describe patterns of cannabis use, the degree of overlap between medicinal and recreational users, and their differential use patterns, modes of consumption and sources of cannabis.

A total of 2,009 individuals from Washington (n = 787), Oregon (n = 506), Colorado (n = 503) and New Mexico (n = 213). Post stratification sampling weights were provided so that estimates could be made representative of the household population in each of these states. Respondents were aged between 18 and 91 years, with a mean age of 53 years.

We compare patterns of cannabis consumption for medicinal and recreational users as well as simultaneous use of alcohol and cannabis. We also examine the extent to which patterns of use differ across states that chose to legalize (Washington and Colorado) and those that did not (New Mexico and Oregon).

Rates of life-time medical cannabis use are similar in Colorado and Washington (8.8% and 8.2%) but lower in Oregon and New Mexico (6.5% and 1%). Recreational use is considerably higher than medical use across all states (41%), but highest in Oregon and Washington. Approximately 86% of people who report ever using cannabis for medicinal purposes also use it recreationally. Medical users are more likely to vaporize and consume edibles and report a higher amount (in grams) consumed, and spend more money per month than recreational users. Individuals who use cannabis do not commonly use it with alcohol, irrespective of whether they are consuming cannabis recreationally or medically. Fewer than one in five recreational users report simultaneous use of alcohol and cannabis most or all of the time and fewer than 3% of medicinal users report frequent simultaneous use of alcohol and cannabis.

In the United States, the degree of overlap between medicinal and recreational cannabis users is 86%. Medicinal and recreational cannabis users favor different modes and amounts of consumption. Only a small proportion (12%) of cannabis users usually consume cannabis and alcohol simultaneously, while concurrent use is common among recreational users.

Schizophrenia Research • June 2016

Does cannabidiol have a role in the treatment of schizophrenia?

Gururajan A1, Malone DT2.

1. Department of Anatomy & Neuroscience, University College Cork, Cork, Ireland
2. Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy & Pharmaceutical Sciences, Monash University, Melbourne, Australia
Electronic address: anand.gururajan@ucc.ie

<http://www.ncbi.nlm.nih.gov/pubmed/27374322>

Schizophrenia is a debilitating psychiatric disorder which places a significant emotional and economic strain on the individual and society-at-large. Unfortunately, currently available therapeutic strategies do not provide adequate relief and some patients are treatment-resistant.

In this regard, cannabidiol (CBD), a non-psychoactive constituent of *Cannabis sativa*, has shown significant promise as a potential antipsychotic for the treatment of schizophrenia. However, there is still considerable uncertainty about the mechanism of action of CBD as well as the brain regions which are thought to mediate its putative antipsychotic effects. We argue that further research on CBD is required to fast-track its progress to the clinic and in doing so, we may generate novel insights into the neurobiology of schizophrenia.

Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study

Smith AM1, Mioduszewski O2, Hatchard T2, Byron-Alhassan A2, Fall C2, Fried PA3.

1. University of Ottawa, School of Psychology, Ottawa, ON K1N 6N5, Canada

2. University of Ottawa, School of Psychology, Ottawa, ON K1N 6N5, Canada

3. Carleton University, Department of Psychology, Ottawa, ON, Canada

Electronic address: asmith@uottawa.ca

<http://www.ncbi.nlm.nih.gov/pubmed/27263090>

Understanding the potentially harmful long term consequences of prenatal marijuana exposure is important given the increase in number of pregnant women smoking marijuana to relieve morning sickness. Altered executive functioning is one area of research that has suggested negative consequences of prenatal marijuana exposure into adolescence. Investigating if these findings continue into young adulthood and exploring the neural basis of these effects was the purpose of this research. Thirty one young adults (ages 18-22years) from the longitudinal Ottawa Prenatal Prospective Study (OPPS) underwent functional magnetic resonance imaging (fMRI) during four tasks; 1) Visuospatial 2-Back, 2) Go/NoGo, 3) Letter 2-Back and 4) Counting Stroop task. Sixteen participants were prenatally exposed to marijuana while 15 had no prenatal marijuana exposure. Task performance was similar for both groups but blood flow was significantly different between the groups. This paper presents the results for all 4 tasks, highlighting the consistently increased left posterior brain activity in the prenatally exposed group compared with the control group. These alterations in neurophysiological functioning of young adults prenatally exposed to marijuana emphasizes the importance of education for women in child bearing years, as well as for policy makers and physicians interested in the welfare of both the pregnant women and their offspring's future success.

Lancet Psychiatry • June 2016

Why it is probably too soon to assess the public health effects of legalisation of recreational cannabis use in the USA

Hall W1, Lynskey M2.

1. Centre for Youth Substance Abuse Research, University of Queensland, Herston, QLD, Australia
National Addiction Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK
2. National Addiction Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK
Electronic address: w.hall@uq.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/27374072>

The citizens of four US states-Alaska, Colorado, Oregon, and Washington-have voted to legalise the sale of cannabis to adults for recreational purposes, and more states look likely to follow. Experience with alcohol and tobacco suggests that a for-profit legal cannabis industry will increase use by making cannabis more socially acceptable to use, making it more readily available at a cheaper price, and increasing the number of users and frequency of their use. We argue that it is too early to see the full effects of legalised cannabis policies on use and harm because several factors could delay the full commercialisation of a legal cannabis industry. These factors include restrictions on various licensed producers and sellers, and legal conflicts between Federal and State laws that might provide a brake on the speed and scale of commercialisation in states that have legalised cannabis. Any increases in cannabis use and harm could be minimised if governments introduced public health policies that limited the promotional activities of a legal cannabis industry, restricted cannabis availability to adults, and maintained cannabis prices at a substantial fraction of the black market price. So far, no states have chosen to implement these policies.

Prenatal, perinatal, and adolescent exposure to marijuana: Relationships with aggressive behavior

Barthelemy OJ1, Richardson MA2, Cabral HJ3, Frank DA4.

1,2. Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA

Division of Psychiatry, Boston University School of Medicine, Boston, MA, USA

3. Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

4. Department of Pediatrics, Boston University School of Medicine, Boston, MA, USA

Electronic address: dafrank@bu.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27345271>

This manuscript reviews research exploring the relationship between prenatal, perinatal, and adolescent exposure to marijuana and aggressive behavior, including physical aggression. Areas of inquiry include animal research, as well as human research, on prenatal exposure and on marijuana use during adolescence. Potential psychosocial and psychopharmacological mechanisms are identified, as well as relevant confounds. The prenatal marijuana exposure literature provides minimal support for a direct relationship with aggressive behavior in childhood. The adolescent use literature suggests a marginal (at best) association between acute intoxication and aggressive behavior, and an association between chronic use and aggressive behavior heavily influenced by demographic variables, rather than direct, psychopharmacological mechanisms. Cannabis withdrawal symptoms also may include aggression and anger, but there is little evidence to suggest that these effects are large or specific to withdrawal from marijuana compared to other substances. This review will offer recommendations for clinical care and public policy, as well as important questions for future research.

Health professionals in Flanders perceive the potential health risks of vaping as lower than those of smoking but do not recommend using e-cigarettes to their smoking patients

Van Gucht D1,2, Baeyens F3.

1. Thomas More University College Antwerp and KU Leuven, Antwerp, Belgium

2,3. KU Leuven, Leuven, Belgium

dinska.vangucht@thomasmore.be

Full text with 38 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4919883/>

Many misperceptions of both risks and opportunities of e-cigarettes (e-cigs) exist among the general population and among physicians, although e-cigs could be a valuable harm reduction tool for current smokers.

Two groups in Flanders, namely general practitioners (GPs; family doctors) and tobacco counselors filled out an online questionnaire with regard to their attitudes and risk perceptions concerning e-cigs. Statements included were on the safety and the addictive properties of e-cigs in absolute terms, whereas other items compared e-cigs with regular tobacco cigarettes. Statements about possible “gateway” and “renormalization” effects, selling to minors, and use in public places and on the potential of e-cigs as a smoking cessation aid were also included. Respondents were also asked for the rate at which their patients asked information about e-cigs, if they would recommend e-cigs to their smoking patients, and whether they had information brochures on e-cigs.

About 70 % believed that e-cigs are harmful to vapers, and about half to two thirds believed that e-cigs are carcinogenic, increase cardiovascular risk, and increase the risk of chronic lung disease. Also, a substantial minority incorrectly believed these risks to be no less than those resulting from regular smoking. Ten to almost 20 % disagreed that e-cigs are healthier and represent less risk for the main serious smoking-related diseases than conventional cigarettes. More than half of the respondents disagreed that e-cigs are an effective smoking cessation aid. None (0 %) offered the strongest level of agreement for recommending e-cigs to their clients/patients, but GPs agreed to a lesser degree a bit more often than tobacco counselors. Almost none had information leaflets for potentially interested patients. Finally, the majority of our sample also believed that e-cigs will cause renormalization of smoking and that e-cigs will lead to an uptake of conventional smoking and disagreed with allowing vaping in enclosed public places.

Cannabinoids reverse the effects of early stress on neurocognitive performance in adulthood

Alteba S1, Korem N1, Akirav I2.

1,2. Department of Psychology, University of Haifa, Haifa 3498838, Israel.
irit.akirav@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/27317195>

Early life stress (ES) significantly increases predisposition to psychopathologies. Cannabinoids may cause cognitive deficits and exacerbate the effects of ES. Nevertheless, the endocannabinoid system has been suggested as a therapeutic target for the treatment of stress- and anxiety-related disorders. Here we examined whether cannabinoids administered during “late adolescence” (extensive cannabis use in humans at the ages 18-25) could reverse the long-term adverse effects of ES on neurocognitive function in adulthood. Male and female rats were exposed to ES during post-natal days (P) 7-14, injected with the cannabinoid CB1/2 receptor agonist WIN55,212-2 (WIN; 1.2 mg/kg, i.p.) for 2 wk during late adolescence (P45-60) and tested in adulthood (P90) for working memory, anxiety, and alterations in CB1 receptors (CB1r), and glucocorticoid receptors (GRs) in the stress circuit [hippocampus, prefrontal cortex (PFC), and basolateral amygdala (BLA)]. ES males and females exhibited impaired performance in short-term memory in adulthood in the spatial location and social recognition tasks; males were also impaired in the novel object recognition task. WIN administered during late adolescence prevented these stress-induced impairments and reduced anxiety levels. WIN normalized the ES-induced up-regulation in PFC-GRs and CA1-CB1r in females. In males, WIN normalized the ES-induced up-regulation in PFC-GR and down-regulation in BLA-CB1r. There is a crucial role of the endocannabinoid system in the effects of early life stress on behavior at adulthood. Differences in recognition memory and in the expression of GRs and CB1r in the fear circuit suggest sex differences in the mechanism underlying coping with stress.

Expert Clinical Psychopharmacology • June 2016

Frequent Cannabis Use Is Associated With Reduced Negative Priming Among Females

Albertella L, Le Pelley ME, Copeland J.

<http://www.ncbi.nlm.nih.gov/pubmed/27337025>

This study examined the relationship between cannabis use, sex, and attentional inhibition in a sample of 325 young Australians (194 women and 131 men) aged 14 to 24 years. Participants completed an online assessment, which included self-report measures of alcohol and other drug use, psychological distress, schizotypy, and location-based negative priming. Participants who had never used cannabis ($n = 163$) were compared with occasional ($n = 118$) and frequent ($n = 44$) cannabis users, with frequent use being defined as having used cannabis at least weekly in the past 6 months. There was a significant interaction between sex and cannabis use, with follow-up analyses indicating that frequent cannabis use was associated with reduced negative priming among females only. This study highlights the role of sex in influencing how cannabis use interacts with cognition and suggests that females who use cannabis frequently may be more likely than males to exhibit deficits in attentional inhibition.

Planta Medica • June 2016

Monitoring Metabolite Profiles of *Cannabis sativa* L. Trichomes during Flowering Period Using ¹H NMR-Based Metabolomics and Real-Time PCR

Happyana N1, Kayser O1.

<http://www.ncbi.nlm.nih.gov/pubmed/27336318>

Cannabis sativa trichomes are glandular structures predominantly responsible for the biosynthesis of cannabinoids, the biologically active compounds unique to this plant. To the best of our knowledge, most metabolomic works on *C. sativa* that have been reported previously focused their investigations on the flowers and leaves of this plant. In this study, ¹H NMR-based metabolomics and real-time PCR analysis were applied for monitoring the metabolite profiles of *C. sativa* trichomes, variety Bediol, during the last 4 weeks of the flowering period. Partial least squares discriminant analysis models successfully classified metabolites of the trichomes based on the harvest time. Δ 9-Tetrahydrocannabinolic acid (1) and cannabidiolic acid (2) constituted the vital differential components of the organic preparations, while asparagine, glutamine, fructose, and glucose proved to be their water-extracted counterparts. According to RT-PCR analysis, gene expression levels of olivetol synthase and olivetolic acid cyclase influenced the accumulation of cannabinoids in the *Cannabis* trichomes during the monitoring time. Moreover, quantitative ¹H NMR and RT-PCR analysis of the *Cannabis* trichomes suggested that the gene regulation of cannabinoid biosynthesis in the *C. sativa* variety Bediol is unique when compared with other *C. sativa* varieties.

Yale Journal Of Biological Medicine • June 2016

Marijuana, the Endocannabinoid System and the Female Reproductive System

By L.K. Brents

Department of Pharmacology and Toxicology and Department of Psychiatry, University of Arkansas for Medical Sciences

Full text with 114 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4918871/>

Marijuana use among women is highly prevalent, but the societal conversation on marijuana rarely focuses on how marijuana affects female reproduction and endocrinology. This article reviews the current scientific literature regarding marijuana use and hypothalamic-pituitary-ovarian (HPO) axis regulation, ovarian hormone production, the menstrual cycle, and fertility. Evidence suggests that marijuana can reduce female fertility by disrupting hypothalamic release of gonadotropin releasing hormone (GnRH), leading to reduced estrogen and progesterone production and anovulatory menstrual cycles. Tolerance to these effects has been shown in rhesus monkeys, but the effects of chronic marijuana use on human female reproduction are largely unknown. Marijuana-induced analgesia, drug reinforcement properties, tolerance, and dependence are influenced by ovarian hormones, with estrogen generally increasing and progesterone decreasing sensitivity to marijuana. Carefully controlled regulation of the Endocannabinoid System (ECS) is required for successful reproduction, and the exogenous cannabinoids in marijuana may disrupt the delicate balance of the ECS in the female reproductive system.

Medical marijuana patient counseling points for health care professionals based on trends in the medical uses, efficacy, and adverse effects of cannabis-based pharmaceutical drugs

Parmar JR1, Forrest BD2, Freeman RA2.

1,2. School of Pharmacy and Health Professions, University of Maryland Eastern Shore, Princess Anne, MD 21853, USA
Electronic address: jparmar@umes.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26443472>

The purpose of this report is to present a review of the medical uses, efficacy, and adverse effects of the three approved cannabis-based medications and ingested marijuana. A literature review was conducted utilizing key search terms: dronabinol, nabilone, nabiximols, cannabis, marijuana, smoke, efficacy, toxicity, cancer, multiple sclerosis, nausea, vomiting, appetite, pain, glaucoma, and side effects. Abstracts of the included literature were reviewed, analyzed, and organized to identify the strength of evidence in medical use, efficacy, and adverse effects of the approved cannabis-based medications and medical marijuana. A total of 68 abstracts were included for review. Dronabinol's (Marinol) most common medical uses include weight gain, chemotherapy-induced nausea and vomiting (CINV), and neuropathic pain. Nabiximol's (Sativex) most common medical uses include spasticity in multiple sclerosis (MS) and neuropathic pain. Nabilone's (Cesamet) most common medical uses include CINV and neuropathic pain. Smoked marijuana's most common medical uses include neuropathic pain and glaucoma. Orally ingested marijuana's most common medical uses include improving sleep, reducing neuropathic pain, and seizure control in MS. In general, all of these agents share similar medical uses. The reported adverse effects of the three cannabis-based medications and marijuana show a major trend in central nervous system (CNS)-related adverse effects along with cardiovascular and respiratory related adverse effects. Marijuana shares similar medical uses with the approved cannabis-based medications dronabinol (Marinol), nabiximols (Sativex), and nabilone (Cesamet), but the efficacy of marijuana for these medical uses has not been fully determined due to limited and conflicting literature. Medical marijuana also has similar adverse effects as the FDA-approved cannabis-based medications mainly consisting of CNS related adverse effects but also including cardiovascular and respiratory related adverse effects. Finally, insufficient higher-order evidence to support the widespread use of medical marijuana was found, but a limited amount of moderate-level evidence supports its use in pain and seizure management.

Cannabis Abusers Show Hypofrontality and Blunted Brain Responses to a Stimulant Challenge in Females but not in Males

Wiers CE1, Shokri-Kojori E1, Wong CT1, Abi-Dargham A2, Demiral ŞB1, Tomasi D1, Wang GJ1, Volkow ND1,3.

1. National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

2. Division of Translational Imaging, Department of Psychiatry, Columbia University and New York State Psychiatric Institute, New York, NY, USA

3. National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA

<http://www.ncbi.nlm.nih.gov/pubmed/27156854>

The extent to which cannabis is deleterious to the human brain is not well understood. Here, we test whether cannabis abusers (CA) have impaired frontal function and reactivity to dopaminergic signaling, which are fundamental to relapse in addiction. We measured brain glucose metabolism using PET and [18F]FDG both at baseline (placebo) and after challenge with methylphenidate (MP), a dopamine-enhancing drug, in 24 active CA (50% female) and 24 controls (HC; 50% female). Results show that (i) CA had lower baseline glucose metabolism than HC in frontal cortex including anterior cingulate, which was associated with negative emotionality. (ii) MP increased whole-brain glucose metabolism in HC but not in CA; and group by challenge effects were most profound in putamen, caudate, midbrain, thalamus, and cerebellum. In CA, MP-induced metabolic increases in putamen correlated negatively with addiction severity. (iii) There were significant gender effects, such that both the group differences at baseline in frontal metabolism and the attenuated regional brain metabolic responses to MP were observed in female CA but not in male CA. As for other drug addictions, reduced baseline frontal metabolism is likely to contribute to relapse in CA. The attenuated responses to MP in midbrain and striatum are consistent with decreased brain reactivity to dopamine stimulation and might contribute to addictive behaviors in CA. The gender differences suggest that females are more sensitive than males to the adverse effects of cannabis in brain.

Recent Patents In CNS Drug Discovery • June 2016

Cannabimimetic Drugs: Recent Patents in Central Nervous System Disorders

Ranieri R, Marasco D, Bifulco M, Malfitano AM1.

Department of Medicine and Surgery, University of Salerno, Via Salvatore Allende, Baronissi, 84081 Salerno, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/27334611>

Agents acting via cannabinoid receptors have been widely developed; starting from the chemical structure of phytocannabinoids isolated from cannabis sativa plant, specific and selective compounds of these receptors have been produced ranging from partial to full agonists and /or antagonists endowed with different potency. The enhanced interest on developing such classes of drugs is due to the beneficial properties widely reported by both anecdotal reports and scientific studies describing the potential medicinal use of cannabinoids and their derivatives in numerous pathological conditions in both in vitro and in vivo models. The use of these drugs has been found to be of benefit in a wide number of neurological and neuropsychiatric disorders, and in many other diseases ranging from cancer, atherosclerosis, stroke, hypertension, inflammatory related disorders, and autoimmune diseases, just to mention some. In particular, being the cannabinoid CB1 receptor a central receptor expressed by neurons of the central nervous system, the attention for the treatment of neurological diseases has been mainly focused on compounds acting via this receptor, however some of these compounds has been showed to act by alternative pathways in some cases unrelated to CB1 receptors. Nonetheless, endocannabinoids are potent regulators of the synaptic function in the central nervous system and their levels are modulated in neurological diseases. In this study, we focused on endocannabinoid mechanism of action in neuronal signaling and on cannabimimetic drug potential application in neurological disorders. Finally, novel patents on cannabis-based drugs with applicability in central nervous system disorders are highlighted, to suggest future potential therapeutic utility of derivatives of this ancient plant.

Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry

Orr JM1, Paschall CJ2, Banich MT3.

1. Department of Psychology, Texas A&M University, United States; Institute of Cognitive Science, University of Colorado Boulder, USA

2. Department of Psychology and Neuroscience, University of Colorado Boulder, USA

3. Institute of Cognitive Science, University of Colorado Boulder, United States; Department of Psychology and Neuroscience, University of Colorado Boulder, USA

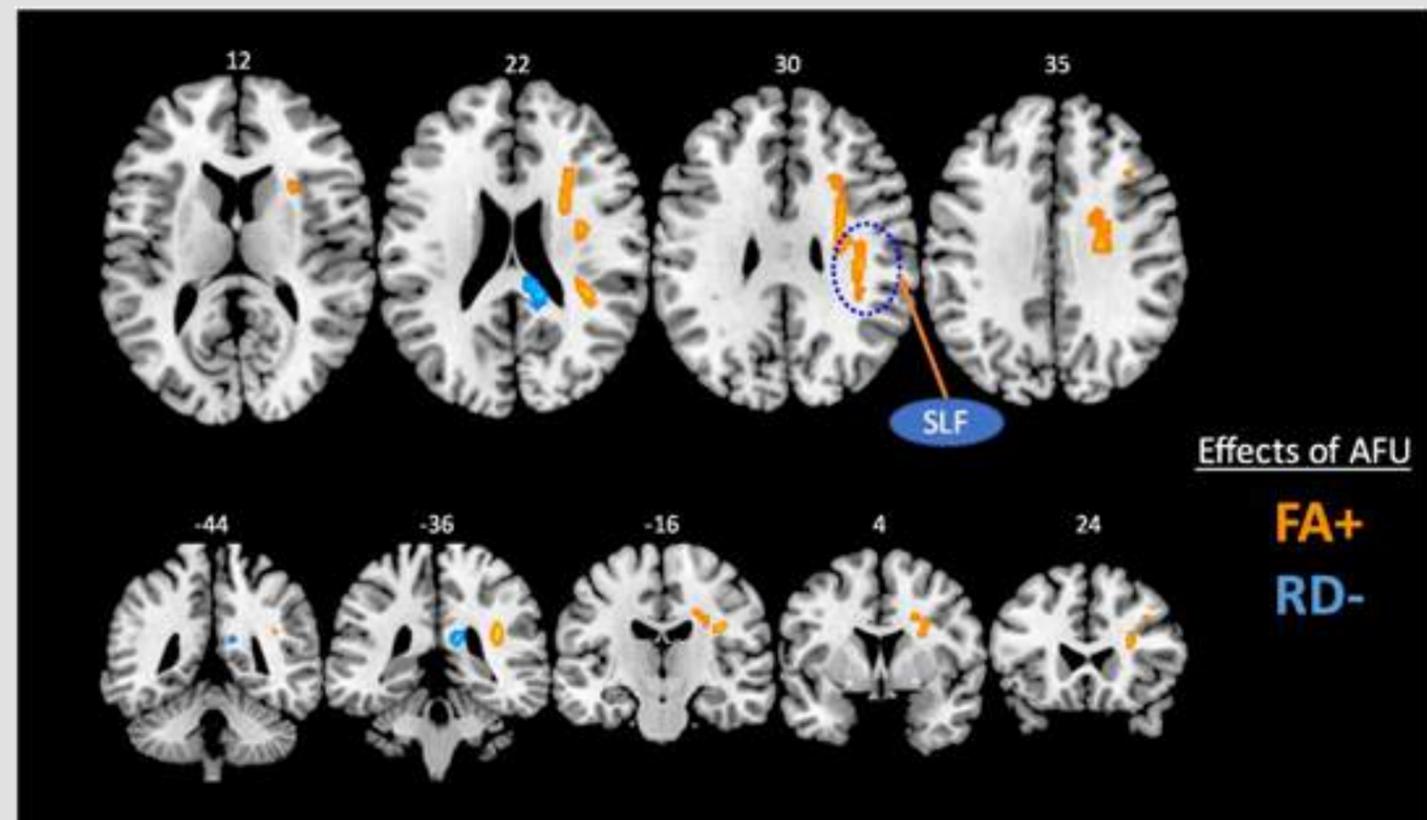
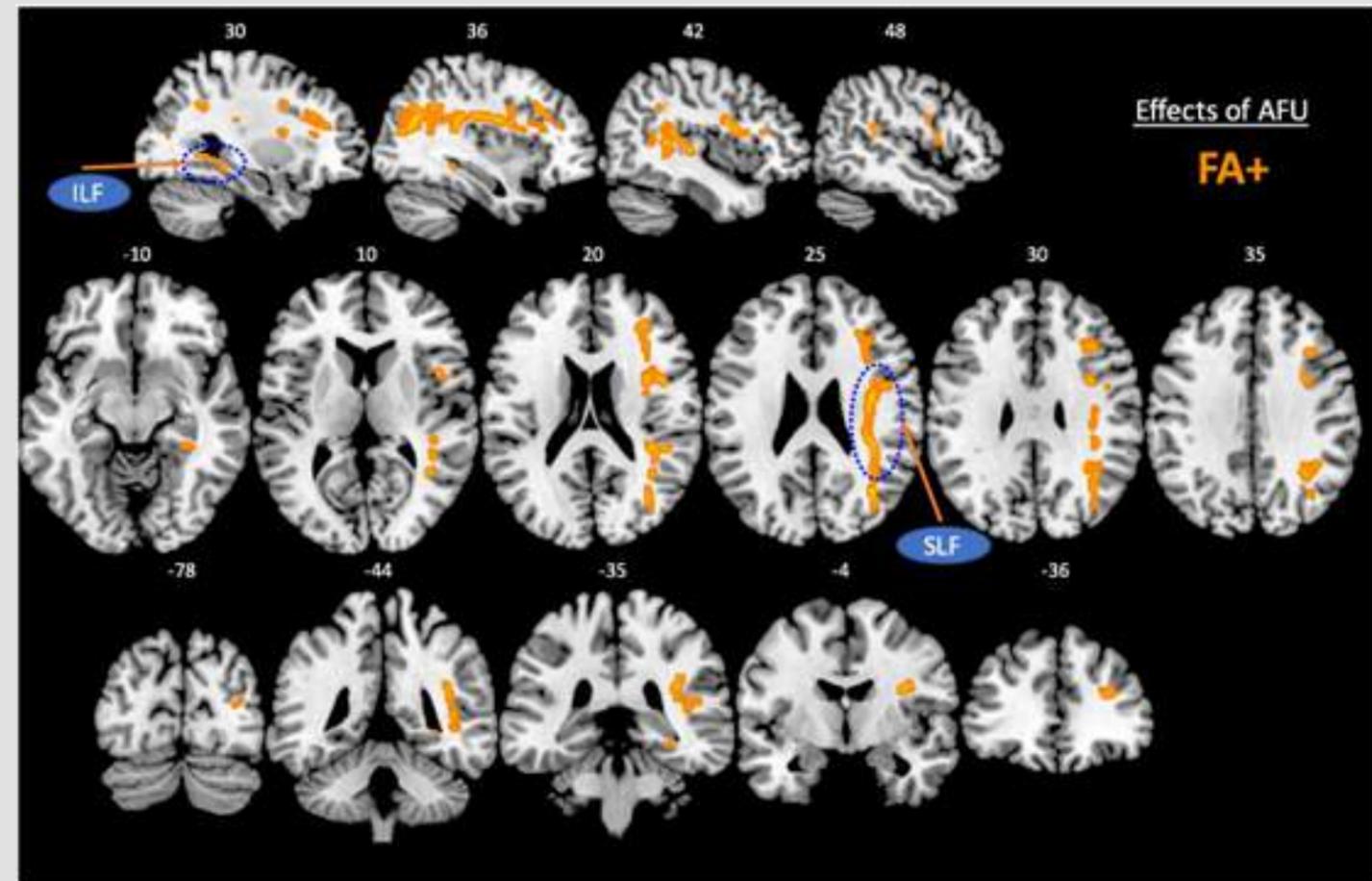
Full text with 62 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4925620/>

A recent shift in legal and social attitudes toward marijuana use has also spawned a surge of interest in understanding the effects of marijuana use on the brain. There is considerable evidence that an adolescent onset of marijuana use negatively impacts white matter coherence. On the other hand, a recent well-controlled study demonstrated no effects of marijuana use on the morphometry of subcortical or cortical structures when users and non-users were matched for alcohol use. Regardless, most studies have involved small, carefully selected samples, so the ability to generalize to larger populations is limited. In an attempt to address this issue, we examined the effects of marijuana use on white matter integrity and cortical and subcortical morphometry using data from the Human Connectome Project (HCP) consortium. The HCP data consists of ultra-high resolution neuroimaging data from a large community sample, including 466 adults reporting recreational marijuana use. Rather than just contrasting two groups of individuals who vary significantly in marijuana usage as typifies prior studies, we leveraged the large sample size provided by the HCP data to examine parametric effects of recreational marijuana use. Our results indicate that the earlier the age of onset of marijuana use, the lower was white matter coherence. Age of onset also affected the shape of the accumbens, while the number of lifetime uses impacted the shape of the amygdala and hippocampus. Marijuana use had no effect on cortical volumes. These findings suggest subtle but significant effects of recreational marijuana use on brain structure.

MRI Images On Following Page

These images depict the effects of age of first use of marijuana on Tract-Based Spatial Statistics from the full sample of 466 marijuana users. Hot colors depict a positive relationship between age of first use and FA, i.e., earlier age of onset associated with decreased FA, and cold colors depict a negative relationship between age of first use and RD, i.e., earlier age of onset associated with increased RD. Earlier marijuana use was associated with decreased white matter coherence in the right Superior Longitudinal Fasciculus, lateral prefrontal white matter, anterior and posterior corpus callosum (extending to the Forceps Minor and Major), as well as the right Inferior Longitudinal Fasciculus. White numbers reflect MNI coordinates in the Z (axial slices), and Y (coronal slices) planes.



Developmental pathways from prenatal marijuana exposure to Cannabis Use Disorder in young adulthood

Sonon K1, Richardson GA2, Cornelius J2, Kim KH, Day NL3.

1. Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, 130 DeSoto Street, Pittsburgh, PA 15260, USA

2,3. Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA

Electronic address: nday@pitt.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27208888>

Earlier studies reported an association between prenatal marijuana exposure (PME) and cognitive and behavioral problems in the offspring. A recent publication demonstrated the relation between PME and offspring marijuana use at age 22. There are no reports of the association between PME and Cannabis Use Disorder (CUD) at 22years, the age when use of marijuana and CUD peak.

Although there is no direct effect of PME on CUD, there are significant indirect pathways from PME to CUD that affect the rate of CUD in the population. Thus, PME, offspring depression, and an early age of marijuana initiation, are significant points for intervention. As marijuana is legalized in more states, the rates of marijuana use will increase significantly, including during pregnancy, and the consequences of the association between PME and CUD will become even more significant from a public health perspective.

F1000 Research • May 2016

Cannabinoid receptor type-1: breaking the dogmas

Busquets Garcia A1, Soria-Gomez E1, Bellocchio L1, Marsicano G1.

1. Endocannabinoids and Neuroadaptation, INSERM U1215 NeuroCentre Magendie, Bordeaux, France
University Of Bordeaux, Bordeaux, France

Full text with 117 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879932/>

The endocannabinoid system (ECS) is abundantly expressed in the brain. This system regulates a plethora of physiological functions and is composed of cannabinoid receptors, their endogenous ligands (endocannabinoids), and the enzymes involved in the metabolism of endocannabinoids. In this review, we highlight the new advances in cannabinoid signaling, focusing on a key component of the ECS, the type-1 cannabinoid receptor (CB 1). In recent years, the development of new imaging and molecular tools has demonstrated that this receptor can be distributed in many cell types (e.g., neuronal or glial cells) and intracellular compartments (e.g., mitochondria). Interestingly, cellular and molecular effects are differentially mediated by CB 1 receptors according to their specific localization (e.g., glutamatergic or GABAergic neurons). Moreover, this receptor is expressed in the periphery, where it can modulate periphery-brain connections. Finally, the better understanding of the CB 1 receptor structure led researchers to propose interesting and new allosteric modulators. Thus, the advances and the new directions of the CB 1 receptor field will provide new insights and better approaches to profit from its interesting therapeutic profile.

CB2 Cannabinoid Receptor As Potential Target against Alzheimer's Disease

Aso E1, Ferrer I1.

1. Institut de Neuropatologia, Servei d'Anatomia Patològica, Bellvitge Biomedical Research Institute (IDIBELL)-Hospital Universitari de Bellvitge, Universitat de BarcelonaL'Hospitalet de Llobregat, Spain
CIBERNED - Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Instituto Carlos III Madrid, Spain

Full text with 80 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4885828/>

The CB2 receptor is one of the components of the endogenous cannabinoid system, a complex network of signaling molecules and receptors involved in the homeostatic control of several physiological functions. Accumulated evidence suggests a role for CB2 receptors in Alzheimer's disease (AD) and indicates their potential as a therapeutic target against this neurodegenerative disease. Levels of CB2 receptors are significantly increased in post-mortem AD brains, mainly in microglia surrounding senile plaques, and their expression levels correlate with the amounts of A β 42 and β -amyloid plaque deposition. Moreover, several studies on animal models of AD have demonstrated that specific CB2 receptor agonists, which are devoid of psychoactive effects, reduce AD-like pathology, resulting in attenuation of the inflammation associated with the disease but also modulating A β and tau aberrant processing, among other effects. CB2 receptor activation also improves cognitive impairment in animal models of AD. This review discusses available data regarding the role of CB2 receptors in AD and the potential usefulness of specific agonists of these receptors against AD.

The association of specific traumatic experiences with cannabis initiation and transition to problem use: Differences between African-American and European-American women

Werner KB¹, McCutcheon VV², Agrawal A², Sartor CE³, Nelson EC², Heath AC², Bucholz KK².

1. George Warren Brown School of Social Work, Washington University, St. Louis, MO, USA
2. Alcohol Research Center, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
3. Alcohol Research Center, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
Electronic address: kbwerner@wustl.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27012434>

Analyses revealed different trauma-related and psychiatric predictors for cannabis use supporting racially distinct etiologic models of cannabis involvement. For AA women, history of witnessing injury/death or experiencing a life-threatening accident was associated with cannabis initiation across the complete emerging adult risk period while sexual abuse predicted cannabis initiation only before 15 years old. For EA women, history of sexual or physical abuse and major depressive disorder (MDD) predicted cannabis initiation and physical abuse and MDD predicted transition from initiation to first CUD symptom. No association was discovered

Results reveal trauma exposures as important contributors to cannabis initiation and to a lesser extent transition to CUD symptom, with different trauma types conferring risk for cannabis involvement in AA and EA women. Findings suggest the importance of considering racial/ethnic differences when developing etiologic models of cannabis involvement.

Grey Matter Changes Associated with Heavy Cannabis Use: A Longitudinal sMRI Study

Koenders L1, Cousijn J1,2,3, Vingerhoets WA4,5, van den Brink W1, Wiers RW2,6, Meijer CJ1, Machielsen MW1, Veltman DJ7, Goudriaan AE1,8, de Haan L1.

1. Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
2. Addiction Development and Psychopathology (ADAPT)-lab, Department of Developmental Psychology, University of Amsterdam, Amsterdam, The Netherlands
3. Department of Developmental Psychology and Psychonomics, Utrecht University, Utrecht, The Netherlands
4. Department of Nuclear Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
5. Department of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands
6. Cognitive Science Center Amsterdam, University of Amsterdam, Amsterdam, The Netherlands
7. University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
8. Arkin Mental Health Care, Amsterdam, The Netherlands

Full text with 51 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4880314/>

Cannabis is the most frequently used illicit drug worldwide. Cross-sectional neuroimaging studies suggest that chronic cannabis exposure and the development of cannabis use disorders may affect brain morphology. However, cross-sectional studies cannot make a conclusive distinction between cause and consequence and longitudinal neuroimaging studies are lacking. In this prospective study we investigate whether continued cannabis use and higher levels of cannabis exposure in young adults are associated with grey matter reductions. Heavy cannabis users ($N = 20$, age baseline $M = 20.5$, $SD = 2.1$) and non-cannabis using healthy controls ($N = 22$, age baseline $M = 21.6$, $SD = 2.45$) underwent a comprehensive psychological assessment and a T1- structural MRI scan at baseline and 3 years follow-up. Grey matter volumes (orbitofrontal cortex, anterior cingulate cortex, insula, striatum, thalamus, amygdala, hippocampus and cerebellum) were estimated using the software package SPM (VBM-8 module). Continued cannabis use did not have an effect on GM volume change at follow-up. Cross-sectional analyses at baseline and follow-up revealed consistent negative correlations between cannabis related problems and cannabis use (in grams) and regional GM volume of the left hippocampus, amygdala and superior temporal gyrus. These results suggests that small GM volumes in the medial temporal lobe are a risk factor for heavy cannabis use or that the effect of cannabis on GM reductions is limited to adolescence with no further damage of continued use after early adulthood. Long-term prospective studies starting in early adolescence are needed to reach final conclusions.

Marijuana use trajectories and academic outcomes among college students

Suerken CK1, Reboussin BA2, Egan KL3, Sutfin EL3, Wagoner KG3, Spangler J4, Wolfson M3.

1,2. Department of Biostatistical Sciences, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA

Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

3. Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

4. Department of Family and Community Medicine, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Electronic address: CSuerken@wakehealth.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27020322>

Marijuana is the most commonly used illicit drug by college students. Prior studies have established an association between marijuana use and poor academic performance in college, but research on the frequency of marijuana use over the entire college career is limited. The study objective was to examine the association of marijuana use trajectories on academic outcomes, including senior year enrollment, plans to graduate on time, and GPA.

Data were collected from a cohort of 3,146 students from 11 colleges in North Carolina and Virginia at six time points across the college career. Group-based trajectory models were used to characterize longitudinal marijuana use patterns during college. Associations between marijuana trajectory groups and academic outcomes were modeled using random-effects linear and logistic regressions.

Five marijuana trajectory groups were identified: non-users (69.0%), infrequent users (16.6%), decreasing users (4.7%), increasing users (5.8%), and frequent users (3.9%). Decreasing users and frequent users were more likely to drop out of college and plan to delay graduation when compared to non-users. All marijuana user groups reported lower GPAs, on average, than non-users.

These results identify marijuana use patterns that put students at risk for poor academic performance in college. Students who use marijuana frequently at the beginning of the college career are especially at risk for lower academic achievement than non-users, suggesting that early intervention is critical.

Endocannabinoid signaling at the periphery: 50 years after THC

Maccarrone M1, Bab I2, Bíró T3, Cabral GA4, Dey SK5, Di Marzo V6, Konje JC7, Kunos G8, Mechoulam R9, Pacher P8, Sharkey KA10, Zimmer A11.

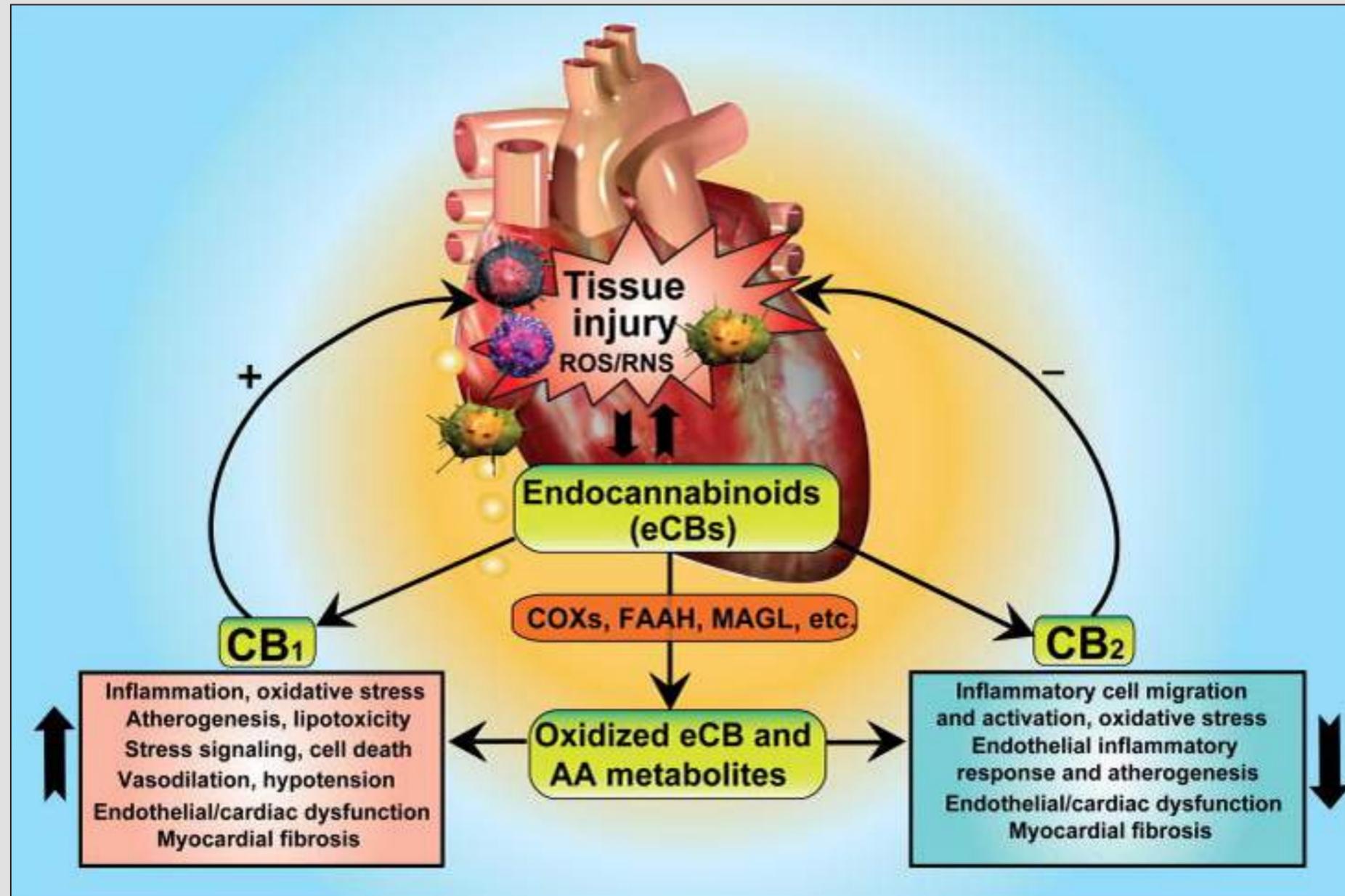
1. Center of Integrated Research, Campus Bio-Medico University, Rome, Italy; Center for Brain Research, Santa Lucia Foundation IRCCS, Rome, Italy
 2. Bone Laboratory, Hebrew University Medical Faculty, Jerusalem, Israel; Institute for Drug Research, Hebrew University Medical Faculty, Jerusalem, Israel
 3. DE-MTA 'Lendület' Cellular Physiology Research Group, Department of Physiology, Medical Faculty, University of Debrecen, Debrecen, Hungary
 4. Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond, VA, USA
 5. Division of Reproductive Sciences, Cincinnati Children's Research Foundation, Cincinnati, OH, USA
 6. Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Council of Research, Pozzuoli, Italy
 7. Department of Obstetrics and Gynaecology, Sidra Medical and Research Center, Doha, Qatar
 8. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA
 9. Institute for Drug Research, Hebrew University Medical Faculty, Jerusalem, Israel
 10. Hotchkiss Brain Institute, Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Alberta, Canada
 11. Institute of Molecular Psychiatry, University of Bonn, Bonn, Germany
- Electronic address: m.maccarrone@unicampus.it

Full text with 180 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4420685/>

In 1964, the psychoactive ingredient of *Cannabis sativa*, $\Delta(9)$ -tetrahydrocannabinol (THC), was isolated. Nearly 30 years later the endogenous counterparts of THC, collectively termed endocannabinoids (eCBs), were discovered: N-arachidonoylethanolamine (anandamide) (AEA) in 1992 and 2-arachidonoylglycerol (2-AG) in 1995. Since then, considerable research has shed light on the impact of eCBs on human health and disease, identifying an ensemble of proteins that bind, synthesize, and degrade them and that together form the eCB system (ECS). eCBs control basic biological processes including cell choice between survival and death and progenitor/stem cell proliferation and differentiation. Unsurprisingly, in the past two decades eCBs have been recognized as key mediators of several aspects of human pathophysiology and thus have emerged to be among the most widespread and versatile signaling molecules ever discovered. Here some of the pioneers of this research field review the state of the art of critical eCB functions in peripheral organs. Our community effort is aimed at establishing consensus views on the relevance of the peripheral ECS for human health and disease pathogenesis, as well as highlighting emerging challenges and therapeutic hopes.

Continued on next page



Role of ECS in cardiovascular injury/disease. Cardiovascular insult inflicted by ischemia, inflammation or hemodynamic overload leads to increased formation of reactive oxygen and/or nitrogen species (ROS/RNS) and inflammation. These processes trigger activation of ECS in cardiovascular system and infiltrating immune cells. eCBs via activation of CB₁ in cardiomyocytes, endothelial cells, fibroblasts and certain immune cells promote processes facilitating development of cardiovascular dysfunction, inflammation and pathological remodeling. In contrast, eCBs via activation of CB₂ exert opposing protective effects. Moreover, eCBs through their catabolism by FAAH and/or MAGL or oxidation by cyclooxygenases (COXs) or other enzymes may represent a significant source of arachidonic acid (AA) and/or other oxidized eCB metabolites with both pro- and anti-inflammatory effects. Thus, the protective or detrimental effect of eCBs in cardiovascular diseases may largely be context-, time- and pathology-dependent.

Cross-generational THC exposure alters the developmental sensitivity of ventral and dorsal striatal gene expression in male and female offspring

Szutorisz H1, Egervári G2, Sperry J1, Carter JM1, Hurd YL3.

1. Friedman Brain Institute, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
2,3. Friedman Brain Institute, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
Friedman Brain Institute, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA
Electronic address: yasmin.hurd@mssm.edu

<http://www.ncbi.nlm.nih.gov/pubmed/27221226>

Cannabis (*Cannabis sativa*, *Cannabis indica*) is the illicit drug most frequently abused by young men and women. The growing use of the drug has raised attention not only on the impact of direct exposure on the developing brain and behavior later in life, but also on potential cross-generational consequences. Our previous work demonstrated that adolescent exposure to Δ^9 -tetrahydrocannabinol (THC), the main psychoactive component of cannabis, affects reward-related behavior and striatal gene expression in male offspring that were unexposed to the drug during their own lifespan. The significant sex differences documented for most addiction and psychiatric disorders suggest that understanding the perturbation of the brain in the two sexes due to cannabis could provide insights about neuronal systems underpinning vulnerability to psychiatric illnesses. In the current study, we expanded our previous observations in males by analyzing the female brain for specific aberrations associated with cross-generational THC exposure. Based on the impact of adolescent development on subsequent adult behavioral pathology, we examined molecular patterns during both adolescence and adulthood. The results revealed a switch from the ventral striatum during adolescence to the dorsal striatum in adulthood in alterations of gene expression related to synaptic plasticity in both sexes. Females, however, exhibited stronger correlation patterns between genes and also showed locomotor disturbances not evident in males. Overall, the findings demonstrate cross-generational consequences of parental THC exposure in both male and female offspring.

Effect of cannabis on glutamate signalling in the brain: A systematic review of human and animal evidence

Colizzi M1, McGuire P1, Pertwee RG2, Bhattacharyya S3.

1,3. Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

2. Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, UK

Electronic address: sagnik.2.bhattacharyya@kcl.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/26987641>

Use of cannabis or delta-9-tetrahydrocannabinol (Δ 9-THC), its main psychoactive ingredient, is associated with psychotic symptoms or disorder. However, the neurochemical mechanism that may underlie this psychotomimetic effect is poorly understood. Although dopaminergic dysfunction is generally recognized as the final common pathway in psychosis, evidence of the effects of Δ 9-THC or cannabis use on dopaminergic measures in the brain is equivocal. In fact, it is thought that cannabis or Δ 9-THC may not act on dopamine firing directly but indirectly by altering glutamate neurotransmission. Here we systematically review all studies examining acute and chronic effects of cannabis or Δ 9-THC on glutamate signalling in both animals and man. Limited research carried out in humans tends to support the evidence that chronic cannabis use reduces levels of glutamate-derived metabolites in both cortical and subcortical brain areas. Research in animals tends to consistently suggest that Δ 9-THC depresses glutamate synaptic transmission via CB1 receptor activation, affecting glutamate release, inhibiting receptors and transporters function, reducing enzyme activity, and disrupting glutamate synaptic plasticity after prolonged exposure.

Neurocognitive Characteristics of Early Marijuana Use Initiation in Adolescents: A Signature Mapping Analysis

Fishbein DH1, Novak SP2, Ridenour TA2, Thornburg V2, Hammond J2, Brown J2.

1. University Park, Pennsylvania

2. RTI International, Research Triangle Park, North Carolina

<http://www.ncbi.nlm.nih.gov/pubmed/27172575>

Prior studies of the association between neurocognitive functions and marijuana use among adolescents are mostly cross-sectional and conducted in adolescents who have already initiated marijuana use. The current study used a longitudinal design on a preadolescent, substance-naive sample. We sought to identify demographic factors associated with neurocognitive functions and the complement of neurocognitive function characteristics that predict marijuana initiation in adolescents.

Substance-naive adolescents (n = 465) ages 10-12 years (51% male) were recruited from a community with high levels of adolescent marijuana use and prospectively followed to ages 12-15. Tasks measuring neurocognitive functions were administered and audio-assisted interviews were conducted. Two types of models were estimated for each outcome: forced-entry models and another using stepwise selection via bidirectional elimination with varying tolerance levels to account for selection misspecification.

About 10% (n = 49) initiated marijuana use over the study period. Child's age, academic achievement, and parental education were associated with baseline neurocognitive functions; namely, positive emotion attributions and lower impulsivity.

Facial recognition-particularly misattribution of sad faces-was the strongest predictor of marijuana initiation, including in the stepwise model (partial OR = 1.3, 95% CI [1.03, 1.63], $p < .05$) that resulted in the best-fitting model.

Prediction of marijuana initiation was improved in stepwise models compared with forced-entry models. Emotion perception appears to be an early developmental risk factor that is prospectively associated with marijuana initiation; as expected, other neurocognitive functions did not play an interactive role. Future studies of the interrelationships between emotion perception and the myriad other factors implicated in marijuana initiation, including neurocognitive functions not measured here, will provide a more comprehensive understanding of risk for marijuana initiation.

Dronabinol for chemotherapy-induced nausea and vomiting unresponsive to antiemetics

May MB1, Glode AE2.

1. Department of Pharmacy, Baptist Health Lexington, Lexington, KY, USA

2. Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

<http://www.ncbi.nlm.nih.gov/pubmed/27274310>

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common symptoms feared by patients, but may be prevented or lessened with appropriate medications. Several antiemetic options exist to manage CINV. Corticosteroids, serotonin receptor antagonists, and neurokinin receptor antagonists are the classes most commonly used in the prevention of CINV. There are many alternative drug classes utilized for the prevention and management of CINV such as antihistamines, benzodiazepines, anticonvulsants, cannabinoids, and dopamine receptor antagonists. Medications belonging to these classes generally have lower efficacy and are associated with more adverse effects. They are also not as well studied compared to the aforementioned agents. This review will focus on dronabinol, a member of the cannabinoid class, and its role in CINV. Cannabis sativa L. (also known as marijuana) contains naturally occurring delta-9-tetrahydrocannabinol (delta-9-THC). The synthetic version of delta-9-THC is the active ingredient in dronabinol that makes dronabinol an orally active cannabinoid. Evidence for clinical efficacy of dronabinol will be analyzed in this review as monotherapy, in combination with ondansetron, and in combination with prochlorperazine.

Cannabis and neuropsychiatry, 1: benefits and risks

Andrade C1.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India
candrade@psychiatrist.com

Full text with 23 references

<http://www.psychiatrist.com/jcp/article/Pages/2016/v77n05/v77n0501.aspx>

Cannabis is popularly believed to be a relatively benign substance. Cannabis is also considered to have potential medical benefits, and medical marijuana has been legislated in many parts of the world.

However, a recent meta-analysis found that cannabinoids were associated with only modest benefits for chemotherapy-related nausea and vomiting, small and inconsistent benefits for pain and spasticity, and inconclusive benefits for other indications such as improvement of appetite and weight, reduction in tic severity, and improvement of mood or sleep.

On the flip side, cannabinoids and cannabis have acute and long-term adverse effects. In randomized controlled trials, cannabinoids increase the risk of total adverse events, serious adverse events, and dropout due to adverse events. Cannabis impairs cognition, and driving after cannabis use is associated with an increased risk of traffic accidents, including fatal accidents. Long-term cannabis use may lead to dependence, respiratory conditions, psychosis, and possibly cancer, as well.

Cannabis use during pregnancy may compromise certain pregnancy outcomes such as fetal growth, and use during adolescence may compromise neurodevelopment, social adjustment, and vocational success. The composition and bioavailability of cannabis vary across preparations of the substance and routes of administration; this limits the ability to generalize the findings of studies.

The findings of older research may no longer apply to current strains of cannabis that are higher in psychotogenic content. It is important for medical professionals and the lay public to understand the limitations of the efficacy data and the seriousness of the risks associated with cannabis use in medical and recreational contexts.

Drug vaping applied to cannabis: Is “Cannavaping” a therapeutic alternative to marijuana?

Varlet V1, Concha-Lozano N2, Berthet A2, Plateel G2, Favrat B3,4, De Cesare M3, Lauer E1, Augsburg M1, Thomas A1,5, Giroud C1.

1. Forensic Toxicology and Chemistry Unit, University Centre of Legal Medicine, Geneva-Lausanne, Switzerland
2. Institute for Work and Health (IST), University of Lausanne, University of Geneva, Lausanne, Switzerland
3. Psychology and Traffic Medicine Unit, University Centre of Legal Medicine, Lausanne, Switzerland
4. Department of Ambulatory Care and Community Medicine, University of Lausanne, Switzerland
5. Faculty of Biology and Medicine, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland

Full text with 43 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4881394/>

Therapeutic cannabis administration is increasingly used in Western countries due to its positive role in several pathologies. Dronabinol or tetrahydrocannabinol (THC) pills, ethanolic cannabis tinctures, oromucosal sprays or table vaporizing devices are available but other cannabinoids forms can be used.

Inspired by the illegal practice of dabbing of butane hashish oil (BHO), cannabinoids from cannabis were extracted with butane gas, and the resulting concentrate (BHO) was atomized with specific vaporizing devices. The efficiency of “cannavaping,” defined as the “vaping” of liquid refills for e-cigarettes enriched with cannabinoids, including BHO, was studied as an alternative route of administration for therapeutic cannabinoids.

The results showed that illegal cannavaping would be subjected to marginal development due to the poor solubility of BHO in commercial liquid refills (especially those with high glycerin content). This prevents the manufacture of liquid refills with high BHO concentrations adopted by most recreational users of cannabis to feel the psychoactive effects more rapidly and extensively. Conversely, “therapeutic cannavaping” could be an efficient route for cannabinoids administration because less concentrated cannabinoids-enriched liquid refills are required. However, the electronic device marketed for therapeutic cannavaping should be carefully designed to minimize potential overheating and contaminant generation.

Recent Patents In CNS Drug Discovery • May 2016

Phytocannabinoids and cannabimimetic drugs: recent patents in central nervous system disorders

Ranieri R, Marasco D, Bifulco M, Malfitano AM1.

Department of Medicine and Surgery, University of Salerno, Via Salvatore Allende, Baronissi, 84081 Salerno, Italy
and Department of Pharmacy, University of Salerno, Via Giovanni Paolo II 84084 Fisciano (Salerno), Italia
amalfitano@unisa.it

<http://www.ncbi.nlm.nih.gov/pubmed/27184693>

Starting from the chemical structure of phytocannabinoids, isolated from *Cannabis sativa* plant, research groups designed numerous cannabimimetic drugs. These compounds according to their activities can be partial, full agonists and antagonists of cannabinoid receptors. Anecdotal reports and scientific studies described beneficial properties of cannabinoids and their derivatives in several pathological conditions like neurological and neuropsychiatric disorders, and in many other diseases ranging from cancer, atherosclerosis, stroke, hypertension, inflammatory related disorders, and autoimmune diseases.

Finally, although the study of the mechanisms of action of these compounds is still unsolved, many reports and patents strongly suggest therapeutic potential of these compounds in neurological diseases.

Medical cannabis: considerations for the anesthesiologist and pain physician

Beaulieu P1,2, Boulanger A3,4, Desroches J5, Clark AJ6.

1. Department of Anesthesiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada
2. Department of Anesthesiology, CHUM, 3840 rue St Urbain, Montreal, QC, H2W 1T8, Canada
3. Department of Anesthesiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada
4. Pain Clinic, CHUM, Montréal, QC, Canada
5. Department of Anesthesiology, CHUM, 3840 rue St Urbain, Montreal, QC, H2W 1T8, Canada
6. Department of Anesthesia, Pain Management and Perioperative Medicine, Dalhousie University and Central Zone, Nova Scotia Health Authority - QEII HSC, Halifax, NS, Canada
pierre.beaulieu@umontreal.ca.

<http://www.ncbi.nlm.nih.gov/pubmed/26850063>

New regulations are in place at the federal and provincial levels in Canada regarding the way medical cannabis is to be controlled. The science of medical cannabis and the need for education of healthcare professionals and patients require continued effort. Although cannabinoids work to decrease pain, there is still a need to confirm these beneficial effects clinically and to exploit them with acceptable benefit-to-risk ratios.

**Medicinal cannabis:
Principal cannabinoids concentration and their stability evaluated by a high performance liquid chromatography
coupled to diode array and quadrupole time of flight mass spectrometry method**

Citti C1, Ciccarella G1, Braghiroli D2, Parenti C2, Vandelli MA2, Cannazza G3.

1. Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Via per Monteroni, 73100 Lecce, Italy
CNR NANOTEC, Campus Ecotekne dell'Università del Salento, Via per Monteroni, 73100 Lecce, Italy
2. Dipartimento di Scienze della Vita, Università di Modena e Reggio Emilia, Via Campi 103, 41125 Modena, Italy
3. CNR NANOTEC, Campus Ecotekne dell'Università del Salento, Via per Monteroni, 73100 Lecce, Italy
Dipartimento di Scienze della Vita, Università di Modena e Reggio Emilia, Via Campi 103, 41125 Modena, Italy
Electronic address: giuseppe.cannazza@unimore.it

<http://www.ncbi.nlm.nih.gov/pubmed/27268223>

In the last few years, there has been a boost in the use of cannabis-based extracts for medicinal purposes, although their preparation procedure has not been standardized but rather decided by the individual pharmacists. The present work describes the development of a simple and rapid high performance liquid chromatography method with UV detection (HPLC-UV) for the qualitative and quantitative determination of the principal cannabinoids (CBD-A, CBD, CBN, THC and THC-A) that could be applied to all cannabis-based medicinal extracts (CMEs) and easily performed by a pharmacist. In order to evaluate the identity and purity of the analytes, a high-resolution mass spectrometry (HPLC-ESI-QTOF) analysis was also carried out. Full method validation has been performed in terms of specificity, selectivity, linearity, recovery, dilution integrity and thermal stability. Moreover, the influence of the solvent (ethyl alcohol and olive oil) was evaluated on cannabinoids degradation rate. An alternative extraction method has then been proposed in order to preserve cannabis monoterpene component in final CMEs.

Cannabidiol Counteracts Amphetamine-Induced Neuronal and Behavioral Sensitization of the Mesolimbic Dopamine Pathway through a Novel mTOR/p70S6 Kinase Signaling Pathway

Renard J1, Loureiro M1, Rosen LG1, Zunder J1, de Oliveira C2, Schmid S2, Rushlow WJ3, Laviolette SR4.

1. Addiction Research Group, Department of Anatomy and Cell Biology, and

2. Department of Anatomy and Cell Biology, and

3,4. Addiction Research Group, Department of Anatomy and Cell Biology, and Department of Psychiatry, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario N6A 5C1, Canada
Steven.Laviolette@schulich.uwo.ca

<http://www.ncbi.nlm.nih.gov/pubmed/27147666>

Schizophrenia-related psychosis is associated with disturbances in mesolimbic dopamine (DA) transmission, characterized by hyperdopaminergic activity in the mesolimbic pathway. Currently, the only clinically effective treatment for schizophrenia involves the use of antipsychotic medications that block DA receptor transmission. However, these medications produce serious side effects leading to poor compliance and treatment outcomes. Emerging evidence points to the involvement of a specific phytochemical component of marijuana called cannabidiol (CBD), which possesses promising therapeutic properties for the treatment of schizophrenia-related psychoses. However, the neuronal and molecular mechanisms through which CBD may exert these effects are entirely unknown.

The cannabis-derived phytochemical, cannabidiol (CBD), has been shown to have pharmacotherapeutic efficacy for the treatment of schizophrenia. However, the mechanisms by which CBD may produce antipsychotic effects are entirely unknown. Using preclinical behavioral procedures combined with molecular analyses and in vivo neuronal electrophysiology, our findings identify a functional role for the nucleus accumbens as a critical brain region whereby CBD can produce effects similar to antipsychotic medications by triggering molecular signaling pathways associated with the effects of classic antipsychotic medications. Specifically, we report that CBD can attenuate both behavioral and dopaminergic neuronal correlates of mesolimbic dopaminergic sensitization, via a direct interaction with mTOR/p70S6 kinase signaling within the mesolimbic pathway.

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Dr Prof Orrin Devinsky, MD, et al.

Full text with 26 references

[http://www.thelancet.com/pdfs/journals/lanneur/PIIS1474-4422\(15\)00379-8.pdf](http://www.thelancet.com/pdfs/journals/lanneur/PIIS1474-4422(15)00379-8.pdf)

Almost a third of patients with epilepsy have a treatment-resistant form, which is associated with severe morbidity and increased mortality. Cannabis-based treatments for epilepsy have generated much interest, but scientific data are scarce. We aimed to establish whether addition of cannabidiol to existing anti-epileptic regimens would be safe, tolerated, and efficacious in children and young adults with treatment-resistant epilepsy.

In this open-label trial, patients (aged 1–30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy, who were receiving stable doses of antiepileptic drugs before study entry, were enrolled in an expanded-access programme at 11 epilepsy centres across the USA. Patients were given oral cannabidiol at 2–5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site). The primary objective was to establish the safety and tolerability of cannabidiol and the primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. The efficacy analysis was by modified intention to treat. Comparisons of the percentage change in frequency of motor seizures were done with a Mann-Whitney U test. Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis, and 137 (64%) patients were included in the efficacy analysis. In the safety group, 33 (20%) patients had Dravet syndrome and 31 (19%) patients had Lennox-Gastaut syndrome. The remaining patients had intractable epilepsies of different causes and type. Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhoea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). The median monthly frequency of motor seizures was 30.0 (IQR 11.0–96.0) at baseline and 15.8 (5.6–57.6) over the 12 week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR 0–64.7).

Our findings suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy. Randomised controlled trials are warranted to characterise the safety profile and true efficacy of this compound.

Cannabidiol in patients with treatment-resistant epilepsy

Prisca R Bauer, Josemir W Sander

University of Sheffield, Sheffield, S10 2HQ, UK
c.j.mcdermott@sheffield.ac.uk

JWS has been consulted by and received fees for lectures from GSK, Lunbeck, Teva, Eisai, and UCB Pharma. PRB declares no competing interests.

Full text, PDF, with references

[http://www.thelancet.com/pdfs/journals/lanneur/PIIS1474-4422\(16\)00118-6.pdf](http://www.thelancet.com/pdfs/journals/lanneur/PIIS1474-4422(16)00118-6.pdf)

We read with interest the results reported by Orrin Devinsky and colleagues¹ of an open-label trial of cannabidiol in people with refractory epilepsy. This is a sensitive topic for many, as there are high expectations for cannabidiol as a potential therapy for epilepsy. Some of these expectations have been fuelled by the media. Unlike other compounds which are conventionally trialled away from the public eye, cannabidiol is already legally available in some countries. Promising case reports² have encouraged demand for cannabidiol, however, little is known about its safety and efficacy, making the study by Devinsky and colleagues particularly timely.

An overall seizure reduction of almost 50% compared with baseline is reported in this study. The analysis suggests that about a third of participants had an increased seizure frequency during the treatment period, and another third had less than 50% seizure reduction. Patients often start or switch antiepileptic drugs at times of an exacerbation of seizure frequency. Figure 3 seems to show a regression to the mean that can partly be attributed to the natural course of the condition, and which is inadequately controlled for by the short baseline period of this study. A baseline period of 4 weeks seems too short, especially as the lowest seizure frequency was 11 motor seizures per month. A natural variation in seizure frequency of one or two seizures per month could explain a 10–20% change either way. Adverse events are reported in 78% and serious adverse events in 30% of the participants in the 12 week treatment period. The authors conclude that “cannabidiol has an adequate safety profile”. Compared with other antiepileptic drugs in refractory epilepsy, the number of serious adverse events reported seems high.³ This high frequency might be explained by epilepsy severity in this population, but such an interpretation cannot be assessed with the design of this study.

What this study does show is that, contrary to what many hope, cannabidiol is probably not the magic bullet for severe childhood epilepsy. Properly randomised controlled trials to assess the safety profile and efficacy of cannabidiol are similar to those of other antiepileptic drugs, or worse.

Cannabidiol in patients with treatment-resistant epilepsy

David E Mandelbaum

[thelancet.com/journals/lanneur/article/PIIS1474-4422\(16\)00122-8/fulltext](http://thelancet.com/journals/lanneur/article/PIIS1474-4422(16)00122-8/fulltext)

Orrin Devinsky and colleagues¹ note that cannabidiol is a potent inhibitor of CYP3A4 and CYP2C19, in addition to other cytochrome P isozymes, with the potential to increase serum concentrations of background antiepileptic drugs and their active metabolites.¹ In fact, the effect of cannabidiol on serum clobazam concentrations was well documented in a study;² in 33 patients taking a 5 mg/kg dose of cannabidiol in addition to an average of three different antiepileptic drugs, serum clobazam concentrations rose a median of 10% after cannabidiol was added. Of the 33 patients, 17 were taking clobazepam, and seven of these 17 had an increase of more than 40% in their serum clobazam concentration.² Devinsky and colleagues cite this in their Article, but why were these compelling data not considered in the discussion? Furthermore, the efficacy of clobazam in patients with Lennox-Gastaut syndrome has been shown to have a dose-response curve; raising clobazam concentrations is highly likely to have an effect on seizure frequency.³

The authors report that in their study that roughly a quarter of patients (27%) not taking clobazam also had a reduction in motor seizures of 50% or more. However, in their discussion of placebo response in trials of cannabis-derived treatments the authors note that among findings from 32 randomised controlled trials of add-on treatment in patients with epilepsy, children had a significantly higher response to placebo (19%) than did adults (9.9–15.2%). Furthermore, five studies in patients with Lennox-Gastaut syndrome have also shown that the placebo response for a greater than 50% reduction in seizure frequency was about 19%. Is a response (50% or more reduction in seizure frequency) by 27% of the participants in Devinsky's trial, which was half the percentage of responders in the group taking clobazam, sufficiently different from the 19% of patients that have been shown to respond to a placebo to dismiss the notion that the demonstrated efficacy of cannabidiol is all attributable to increased clobazam concentrations?

I, like all of us dealing with refractory epilepsy, am eager for more effective therapies. I would be delighted if cannabidiol is shown, in a meaningful, interpretable, double-blind study, with clobazam removed as a confounding factor, to be safe and effective. In Bertolt Brecht's *Galileo*, Galileo says to his assistant: "my intention is not to prove I was right but to find out whether I was right"... "and if we find anything which would suit us, that thing we will eye with particular distrust".⁴ The authors, and readers, of this Article would do well to have scientific "distrust" of these data.

Variability in Seed Traits in a Collection of *Cannabis sativa* L. Genotypes

Galasso I1, Russo R1, Mapelli S1, Ponzoni E1, Brambilla IM1, Battelli G2, Reggiani R1.

1. Institute of Agricultural Biology and Biotechnology, CNR Milano, Italy
2. Institute of Science of Food Production, CNR Milano, Italy

Full text with 47 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4873519/>

The seed of *Cannabis sativa* L. is an expanding source of proteins and oil for both humans and animals. In this study, the proximate composition of a collection of hemp cultivars and accessions of different geographical origins grown under the same conditions for 1 year was analyzed in order to identify potential accessions to improve hemp cultivars.

Fatty acids, tocopherols, and antinutritional components, as well as concentrations of crude protein and oil were quantified. The seed oil concentrations varied between 285 and 360 g kg⁻¹ dry seed (DS), while crude protein ranged between 316 and 356 g kg⁻¹ dry matter (DM). The seed oil was mainly composed of unsaturated fatty acids and, as expected, the dominant fatty acids were linoleic and α -linolenic acid. A high variability among the cultivars and accessions was also detected for polyphenolic content which ranged from 5.88 to 10.63 g kg⁻¹ DM, cv. Felina was the richest, whereas cv. Finola had the lowest polyphenolic content. Regarding antinutritional compounds in seed, a high variability was detected among all genotypes analyzed and phytic acid was particularly abundant (ranging between 43 and 75 g kg⁻¹ DM). In conclusion, our results reveal noticeable differences among hemp seed genotypes for antinutritional components, oil and protein content.

Collectively, this study suggests that the hemp seed is an interesting product in terms of protein, oil and antioxidant molecules but a reduction of phytic acid would be desirable for both humans and monogastric animals. The high variability detected among the different genotypes indicates that an improvement of hemp seed might be possible by conventional and/or molecular breeding.

Plant-Derived and Endogenous Cannabinoids in Epilepsy

Verrotti A1, Castagnino M2, Maccarrone M3,4, Fezza F5,6.

1. Department of Pediatrics, University of L'Aquila, Ospedale "San Salvatore", 67100, L'Aquila, Italy
2. Department of Pediatrics, University of Perugia, Ospedale "Santa Maria della Misericordia", Sant'Andrea Delle Fratte, 06123, Perugia, Italy
3. Department of Medicine, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128, Rome, Italy
4. European Center for Brain Research/IRCCS Santa Lucia Foundation, Via del Fosso del Fiorano, 65, 00143, Rome, Italy
5. European Center for Brain Research/IRCCS Santa Lucia Foundation, Via del Fosso del Fiorano, 65, 00143, Rome, Italy
6. Department of Experimental Medicine and Surgery, Tor Vergata University of Rome, Via Montpellier 1, 00130, Rome, Italy

averrott@unich.it.

Filomena.fezza@uniroma2.it

<http://www.ncbi.nlm.nih.gov/pubmed/26892745>

Cannabis is one of the oldest psychotropic drugs and its anticonvulsant properties have been known since the last century. The aim of this review was to analyze the efficacy of cannabis in the treatment of epilepsy in adults and children. In addition, a description of the involvement of the endocannabinoid system in epilepsy is given in order to provide a biochemical background to the effects of endogenous cannabinoids in our body. General tolerability and adverse events associated with cannabis treatment are also investigated. Several anecdotal reports and clinical trials suggest that in the human population cannabis has anticonvulsant properties and could be effective in treating partial epilepsies and generalized tonic-clonic seizures, still known as "grand mal." They are based, among other factors, on the observation that in individuals who smoke marijuana to treat epilepsy, cessation of cannabis use precipitates the re-emergence of convulsive seizures, whereas resuming consumption of this psychotropic drug controls epilepsy in a reproducible manner. In conclusion, there is some anecdotal evidence for the potential efficacy of cannabis in treating epilepsy. Though there has been an increased effort by patients with epilepsy, their caregivers, growers, and legislators to legalize various forms of cannabis, there is still concern about its efficacy, relative potency, availability of medication-grade preparations, dosing, and potential short- and long-term side effects, including those on prenatal and childhood development.

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Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization

By G. S. Wang

Department of Pediatrics, University of Colorado Anschutz Medical Campus, 13123 E 16th Ave B251, Aurora, CO, 80045, USA
George.wang@childrenscolorado.org

<http://www.ncbi.nlm.nih.gov/pubmed/27139708>

An “unintended consequence” of marijuana legalization is the impact on the pediatric population. From pre-natal exposure to unintentional childhood exposures, through concerns of adolescence abuse and marijuana use for medicinal indications in children, marijuana exposure can affect pediatric patients at every stage in childhood. Regardless of the stage or reason of exposure, concerns exist about short-term and long-term consequences in a child’s physical and mental health. The use of cannabidiol (CBD) may have some benefit for the treatment of epilepsy, but emphasis needs to be on rigorous clinical trials to evaluate efficacy and safety. As more states allow both medical and recreational marijuana, availability and prevalence of use will likely increase and more surveillance and research is needed to evaluate the consequences on the pediatric population.

Cannabinoids: Medical implications

Schrot RJ1,2, Hubbard JR3,4.

1. Veterans' Administration Medical Center, Outpatient Clinic, Tampa, FL, USA
2. Department of Family Medicine, University of South Florida, Morsani College of Medicine, Tampa, FL, USA
3. Psychiatry South, Tuscaloosa, AL, USA
4. Indian Rivers Mental Health Clinic, Tuscaloosa, AL, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26912385>

Herbal cannabis has been used for thousands of years for medical purposes. With elucidation of the chemical structures of tetrahydrocannabinol (THC) and cannabidiol (CBD) and with discovery of the human endocannabinoid system, the medical usefulness of cannabinoids has been more intensively explored. While more randomized clinical trials are needed for some medical conditions, other medical disorders, like chronic cancer and neuropathic pain and certain symptoms of multiple sclerosis, have substantial evidence supporting cannabinoid efficacy. While herbal cannabis has not met rigorous FDA standards for medical approval, specific well-characterized cannabinoids have met those standards. Where medical cannabis is legal, patients typically see a physician who "certifies" that a benefit may result. Physicians must consider important patient selection criteria such as failure of standard medical treatment for a debilitating medical disorder. Medical cannabis patients must be informed about potential adverse effects, such as acute impairment of memory, coordination and judgment, and possible chronic effects, such as cannabis use disorder, cognitive impairment, and chronic bronchitis. In addition, social dysfunction may result at work/school, and there is increased possibility of motor vehicle accidents. Novel ways to manipulate the endocannabinoid system are being explored to maximize benefits of cannabinoid therapy and lessen possible harmful effects. Key messages The medical disorders with the current best evidence that supports a benefit for cannabinoid use are the following: multiple sclerosis patient-reported symptoms of spasticity (nabiximols, nabilone, dronabinol, and oral cannabis extract), multiple sclerosis central pain or painful spasms (nabiximols, nabilone, dronabinol, and oral cannabis extract), multiple sclerosis bladder frequency (nabiximols), and chronic cancer pain/neuropathic pain (nabiximols and smoked THC). Herbal can-

nabis has not met rigorous US FDA standards for medical approval, while specific well-characterized cannabinoids have met those standards, and more are being studied. However, herbal cannabis is legal for medical use in certain US states/countries, and patients must usually see a physician who "certifies" that a benefit may result. Participating physicians should be knowledgeable about cannabinoids, closely look at the risk/benefit ratio, and consider certain important criteria in selecting a patient, such as: age, severity, and nature of the medical disorder, prior or current serious psychiatric or substance use disorder, failure of standard medical therapy as well as failure of an approved cannabinoid, serious underlying cardiac/pulmonary disease, agreement to follow-up visits, and acceptance of the detailed explanation of potential adverse risks. The limitations of use of medical cannabis include the following potential adverse effects that are discussed with potential patients: acute central nervous system effects such as deficits in memory, judgment, attention, coordination, and perception (such as time and color), anxiety, dysphoria, and psychosis; chronic central nervous system effects such as cannabis use disorder, cognitive and memory deficits, and increased risk of psychosis; pulmonary effects such as chronic bronchitis; social dysfunction, such as work/school; increased risk of accidents, such as motor vehicle accidents; and preliminary data suggest possible risk for acute cardiovascular event, especially with underlying heart disease. The normal human endocannabinoid system is important in the understanding of such issues as normal physiology, cannabis use disorder, and the development of medications that may act as agonists or antagonists to CB1 and CB2. By understanding the endocannabinoid system, it may be possible to enhance the beneficial effects of cannabinoid-related medication, while reducing the harmful effects.

Cannabis-induced psychosis associated with high potency “wax dabs”

Pierre JM1, Gandal M2, Son M3.

1. Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA
Department of Veterans Affairs, VA Greater Los Angeles Healthcare System, Los Angeles, CA
2. Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA
3. College of Medicine, University of Vermont, Burlington, VT
Electronic address: joseph.pierre2@va.gov

<http://www.ncbi.nlm.nih.gov/pubmed/26876313>

With mounting evidence that the risk of cannabis-induced psychosis may be related to both dose and potency of tetrahydrocannabinol (THC), increasing reports of psychosis associated with cannabinoids containing greater amounts of THC are anticipated. We report two cases of emergent psychosis after using a concentrated THC extract known as cannabis “wax,” “oil,” or “dabs” raising serious concerns about its psychotic liability. Although “dabbing” with cannabis wax is becoming increasingly popular in the US for both recreational and “medicinal” intentions, our cases raise serious concerns about its psychotic liability and highlight the importance of understanding this risk by physicians recommending cannabinoids for purported medicinal purposes.

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Medical Marijuana for Epilepsy?

Kolikonda MK1, Srinivasan K1, Enja M1, Sagi V1, Lippmann S1.

Drs. Kolikonda and Sagi are from the Department of Neurology,
Dr. Srinivasan is from the Clinical Translational Research Support Unit,
and Drs. Enja and Lippmann are from the Department of Psychiatry, University of Louisville School of Medicine, Louisville, Kentucky

Full text with 26 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911937/>

Treatment-refractory epilepsy remains an important clinical problem. There is considerable recent interest by the public and physicians in using medical marijuana or its derivatives to treat seizures. The endocannabinoid system has a role in neuronal balance and ictal control. There is clinical evidence of success in diminishing seizure frequencies with cannabis derivatives, but also documentation about exacerbating epilepsy or of no discernible effect. There are lay indications and anecdotal reports of success in attenuating the severity of epilepsy, but without solid investigational corroboration. Marijuana remains largely illegal, and may induce adverse consequences. Clinical applications are not approved, thus are restricted and only recommended in selected treatment unresponsive cases, with appropriate monitoring.

David Casarett's Stoned: A Doctor's Case for Medical Marijuana

By Bradley E. Alger, Ph.D.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4938260/>

With legal cannabis sales at \$5.4 billion in 2015 and expected to rise by another billion this year in the United States, legalization and marijuana's impact on health is a hot topic of national debate. Casarett, a physician at the University of Pennsylvania, immerses himself in the culture, science, and smoke of medical marijuana in order to sort out the truth behind the buzz. Our reviewer, who has authored more than 120 research papers and reviews on the regulation of synaptic inhibition and endocannabinoids, tell us what the author got right, but also overlooked on his journey to learn more about a complex and controversial subject.

David Casarett was a palliative care doctor with an Archie-Bunkereseque level of skepticism regarding medical marijuana. He doubted that marijuana was a medicine, or indeed that it was good for anything, but finally had to admit that he didn't know enough to advise patients who asked about it. Does marijuana "work?" Is it safe? Effective?

This book chronicles Casarett's foray into the world of medical marijuana. It is an engaging, lively, thought-provoking tour seen from the street, not the laboratory; the walk-in clinic, not the ivory tower. The doctor wants to know not only the subject, but also how to explain it to his patients (and readers) in terms that they will understand; how to give them a voice in their own care and be informed medical consumers. In trying to accomplish this, he covers a lot of ground.

Casarett discusses a range of maladies for which marijuana is said to be beneficial—including insomnia, nausea, cachexia, pain, and cancer—in vignettes that begin with an arresting anecdote or personal story of a patient (including himself in one case). He establishes a largely jargon-free scientific/medical context for understanding how marijuana might act in a given case, and sums up his impressions of the evidence. This is advice such as you'd get from a neighbor (who happens to be a doctor) over a beer after a game of

golf: many "possibles" and "maybes," a few numbers, but no charts and graphs; and only a couple of firm answers.

The uncertainty and caveats are unsurprising because many of the experimental studies available are small and not well controlled. Marijuana "seems to be" effective in treating neuropathic pain, "definitely" works for nausea, "probably" improves appetite, and reduces insomnia; it "might be" helpful for anxiety and PTSD; "maybe, someday" we'll know whether it does anything for cancer, but now, nothing. The reader, who may be frustrated by the indefiniteness of his verdicts, is reminded that the scarcity of hard data results from the benighted federal drug policy that still classifies marijuana as a Schedule I drug (dangerous and of no medical value), significantly worse than morphine, cocaine, or amphetamines, which are on the less restrictive Schedule II.

Usually Casarett gives us enough scientific background to clarify his opinions

without overdoing it. His accounts of why marijuana affects different people differently, and how the storage of THC (the psychoactive chemical in cannabis) in body fat can modulate its effects, are two good examples among many. But the book is as much sociology as medicine. Casarett often goes undercover to capture the experience of the individual patient peering in at the medical marijuana subculture. At one point he gets a tutorial in the psychoactive subtleties of marijuana varieties that is as nuanced as the wine recommendations of a sommelier at a tony New York restaurant (Casarett takes it all in, but is a noncustomer.)

He reviews the panoply of forms and delivery methods of cannabis products—besides the standard joints, there are pills, vaporizers (“vape pens”), oils, resins, oral sprays, potables (cannabis-infused beer and wine), and edibles from gummy bears to brownies—and weighs their pros and cons. He recounts his own attempt to treat chronic back pain by smoking a joint on his back porch: it is neither transformative nor a complete nightmare, although one doubts that he’ll go there again. He does answer a commonly asked question: why smoke if you can get cannabinoids in FDA-approved pills, or edibles? In a nutshell: control. Because of the rapid transit

time for THC to go from the lungs to the brain (tens of seconds), an experienced user can titrate his intake to produce just the desired level of symptomatic relief. Taken by mouth, THC has to pass through the GI tract (tens of minutes, with times dependent on what food was eaten and when, etc.) and undergo variable absorption into the blood stream; no wonder the effects of ingested marijuana are less predictable. Couple this lack of control with the disinclination of severely nauseated patients to swallow anything, and one appreciates the appeal of smoking.

Despite the book’s subtitle (“a Doctor’s Case for Medical Marijuana”) this is not a tale of advocacy; the author shuttles evenly between doubt and sympathy. A hilarious visit to a sketchy marijuana clinic/dispensary that will confirm the worst suspicions of die-hard opponents who see the entire medical marijuana movement as a scam, is counterbalanced by moving stories of people who, having tried conventional medications (including morphine) without success, depend on the comfort that they get from marijuana to live a normal life.

Casarett’s authorial instinct for the captivating image occasionally leads him astray: he repeats a story of some canna-

bis-dependent soldiers in the 1940s and their lurid and sometimes violent behavior when compelled to go cold-turkey during assignment to a cannabis-free environment. This anecdote, seemingly right out of the *Reefer Madness* handbook, is used to dramatize the withdrawal symptoms that might accompany cessation of marijuana use, although Casarett acknowledges that this case is atypical (and hardly a controlled study). He is alarmed that nine percent of marijuana users meet the clinical definition of addiction (as compared with 12 percent of alcohol users and 15 percent of heroin users), and takes it as a given that any addiction is bad.

The discussion would have benefited from a more critical analysis. For instance, given the numbers, shouldn’t we promote marijuana use as a way of reducing the overall heroin addiction rate? Or consider what he doesn’t stress: that overdoses of opiates or alcohol are often fatal. In 2014 opiates caused 25,000 deaths (DrugAbuse.gov), and alcohol-poisoning causes 2,200 deaths each year (CDC website), whereas, as Casarett notes, deaths from marijuana overdose are essentially unknown (DrugWarFact). Finally, alcohol consumption was implicated in 10,076 deaths from car crashes in 2013 (CDC website). Despite the presence of millions of recreational users

in the US, there is no evidence that marijuana causes anything like that level of carnage. Nobody is recommending marijuana use as a public health safety measure—you shouldn't operate cars or heavy machinery when stoned—but these are some of the societal complexities that the book skirts.

Given his cautious conclusion that marijuana can be beneficial in some instances, it may come as a surprise that Casarett is not bullish on marijuana's future as a medicine (he considers it an "herbal remedy"), arguing that major pharmaceutical companies are working overtime to find drugs that will be better at treating the disorders that medical marijuana treats, and will not have marijuana's side effects. He cites the case of glaucoma, for which marijuana used to be recommended, but which is now controlled effectively by conventional medications. On the other hand, the discovery of the opioid receptor many years ago prompted confident predictions that opiate drugs would soon be available that would selectively relieve pain without causing euphoric or addictive side-effects. The current epidemic of prescription opiate-drug addiction (and rebound heroin use) in the US is enough to give one pause. Will Big Pharma have better luck in replacing marijuana?

Casarett's engrossing narrative stance, basically as a physician playing the role of educated layman, perhaps leads him to

overemphasize the interactions of the chemicals in marijuana, e.g., THC, CBD (a non-psychoactive extract) with the major cannabinoid receptors, CB1 and CB2, for understanding marijuana's actions. Different drug-receptor interactions do contribute to marijuana's assortment of behavioral effects, but this narrow focus fosters the misperception that "the future of marijuana research" is in the hands of chemists who are tweaking the THC molecule and producing variants ("synthetic cannabinoids") that also activate the CB1/CB2 receptors.

In fact, these variants will potentially interact with a large number of other molecular targets. As a case in point, anandamide, the classic natural CB1 activator ("endocannabinoid") in the body ("the THC inside all of us"), activates a non-cannabinoid receptor, the TRP receptor, more efficiently than it does CB1! We will need to know much more about the molecular targets of synthetic cannabinoids before assigning them a leading role in medical marijuana-type therapies. More significantly, Casarett skips over the myriad issues associated with the highly variable distribution of CB1 receptors across brain regions and functional classes of brain cells.

Admittedly, this is a complicated subject, yet understanding it and figuring out

how to target the cannabinoids correctly to carefully defined subregions will, I believe, ultimately be more relevant for developing marijuana-based therapies, than refining drug-receptor match-ups. Finally, Casarett barely scratches the surface of the exploding field of the endocannabinoid system, exploitation of which will surely be a major direction for the future of medical marijuana. Why worry about exogenous cannabinoids if we can harness the ones we already have on board?

By and large, however, such lapses do not detract from my enthusiasm for the book. It accomplishes what it sets out to do, giving patients and care-givers a balanced, insightful view of medical marijuana in an entertaining, straight-talking way. I found it an enjoyable read and highly recommend it.

Bradley E. Alger, Ph.D., is a professor emeritus in the Department of Physiology at the University of Maryland School of Medicine. He received his Ph.D. in experimental psychology from Harvard University in 1977, and taught and did research at Maryland from 1981 to 2013. In the early 1990s, Alger and Thomas Pitler characterized the first signaling process ultimately found to be mediated by endocannabinoids in the brain. Alger has authored over 120 research papers and reviews, focusing in the past two decades on the regulation of synaptic inhibition and endocannabinoids.

Polyphenolic Compounds and Antioxidant Activity of Cold-Pressed Seed Oil from Finola Cultivar of Cannabis sativa L

Smeriglio A1,2, Galati EM1, Monforte MT1, Lanuzza F3, D'Angelo V1, Circosta C1.

1. Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali, University of Messina, Messina, Italy
2. Fondazione Prof. Antonio Imbesi: Borsa di Ricerca Scuola di Specializzazione in Farmacognosia, University of Messina, Messina, Italy
3. Dipartimento di Economia, University of Messina, Messina, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/27076277>

The aim of this study was to characterize the polyphenolic compounds and antioxidant activity of cold-pressed seed oil from Finola cultivar of industrial hemp (*Cannabis sativa* L.).

Several methodologies have been employed to evaluate the *in vitro* antioxidant activity of Finola hempseed oil (FHSO) and both lipophilic (LF) and hydrophilic fractions (HF). The qualitative and quantitative composition of the phenolic fraction of FHSO was performed by HPLC analyses. From the results is evident that FHSO has high antioxidative activity, as measured by DPPH radical (146.76 mmol of TE/100 g oil), inhibited β -carotene bleaching, quenched a chemically generated peroxy radical *in vitro* and showed high ferrous ion chelating activity. Reactivity towards 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radical cation and ferric-reducing antioxidant power values were 695.2 μ mol of TE/100g oil and 3690.6 μ mol of TE/100g oil respectively. FHSO contains a significant amount of phenolic compounds of which 2780.4 mg of quercetin equivalent/100 g of total flavonoids.

The whole oil showed higher antioxidant activity compared with LF and HF. Our findings indicate that the significant antioxidant properties shown from Finola seed oil might generally depend on the phenolic compounds, especially flavonoids, such as flavanones, flavonols, flavanols and isoflavones.

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Cannabis craving in response to laboratory-induced social stress among racially diverse cannabis users: The impact of social anxiety disorder

Buckner JD¹, Zvolensky MJ², Ecker AH³, Jeffries ER³.

^{1,3}. Department of Psychology, Louisiana State University, Baton Rouge, LA, USA

². Department of Psychology, University of Houston, Houston, TX, USA The University of Texas MD Anderson Cancer Center, Department of Behavioral Science, Houston, TX, USA
jbuckner@lsu.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/26839322>

Social anxiety disorder appears to be a risk factor for cannabis-related problems. Although it is presumed that increases in cannabis craving during elevated social anxiety reflect an intent to cope with greater negative affectivity, it is unclear whether increases in physiological arousal during social stress are related to cannabis craving, especially among those with social anxiety disorder. Similarly, no studies have assessed motivational reasons for cannabis use during elevated social stress. As predicted, cannabis users in the social interaction condition reported greater cannabis craving than those in the reading condition. This effect was particularly evident among those with social anxiety disorder. Although physiological arousal did not moderate the relationship between condition and craving, coping motives were the most common reasons cited for wanting to use cannabis and were reported more among those in the social interaction task. These experimental results uniquely add to a growing literature suggesting the importance of elevated state social anxiety (especially among those with social anxiety disorder) in cannabis use vulnerability processes.

The burden of disease attributable to cannabis use in Canada in 2012

Imtiaz S1,2, Shield KD1,2, Roerecke M1,3, Cheng J1,4, Popova S1,2,3,5, Kurdyak P1,4,6, Fischer B1,6,7, Rehm J1,2,3,6,8.

1. Centre for Addiction and Mental Health, Toronto, Canada
2. Institute of Medical Science, University of Toronto, Toronto, Canada
3. Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
4. Institute for Clinical Evaluative Sciences, Toronto, Canada
5. Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, Canada
6. Department of Psychiatry, University of Toronto, Toronto, Canada
7. Centre for Applied Research in Mental Health and Addiction, Simon Fraser University, Vancouver, Canada
8. Institute for Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany

<http://www.ncbi.nlm.nih.gov/pubmed/26598973>

Cannabis use is associated with several adverse health effects. However, little is known about the cannabis-attributable burden of disease. This study quantified the age-, sex- and adverse health effect-specific cannabis-attributable (1) mortality, (2) years of life lost due to premature mortality (YLLs), (3) years of life lost due to disability (YLDs) and (4) disability-adjusted life years (DALYs) in Canada in 2012.

Using comparative risk assessment methodology, cannabis-attributable fractions were computed using Canadian exposure data and risk relations from large studies or meta-analyses. Outcome data were obtained from Canadian databases and the World Health Organization. The 95% confidence intervals (CIs) were computed using Monte Carlo methodology.

Cannabis use was estimated to have caused 287 deaths (95% CI = 108, 609), 10,533 YLLs (95% CI = 4760, 20,833), 55,813 YLDs (95% CI = 38,175, 74,094) and 66,346 DALYs (95% CI = 47,785, 87,207), based on causal impacts on cannabis use disorders, schizophrenia, lung cancer and road traffic injuries. Cannabis-attributable burden of disease was highest among young people, and males accounted for twice the burden than females.

The cannabis-attributable burden of disease in Canada in 2012 included 55,813 years of life lost due to disability, caused mainly by cannabis use disorders. Although the cannabis-attributable burden of disease was substantial, it was much lower compared with other commonly used legal and illegal substances. Moreover, the evidence base for cannabis-attributable harms was smaller.

Evaluating the public health impacts of legalizing recreational cannabis use in the USA

Hall W1,2, Lynskey M3.

1. Professor and Director, The University of Queensland Centre for Youth Substance Abuse Research, Kings College London, Herston, Queensland, Australia
2. Professor of Addiction Policy, National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, Herston, Queensland, Australia
3. Professor of Adolescent Addiction, National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, Herston, Queensland, Australia

<http://www.ncbi.nlm.nih.gov/pubmed/27082374>

Since 2012 four US states have legalized the retail sale of cannabis for recreational use by adults and more are likely to follow. This report aimed to (1) briefly describe the regulatory regimes so far implemented; (2) outline their plausible effects on cannabis use and cannabis-related harm; and (3) suggest what research is needed to evaluate the public health impact of these policy changes.

We reviewed the drug policy literature to identify: (1) plausible effects of legalizing adult recreational use on cannabis price and availability; (2) factors that may increase or limit these effects; (3) pointers from studies of the effects of legalizing medical cannabis use; and (4) indicators of cannabis use and cannabis-related harm that can be monitored to assess the effects of these policy changes.

Legalization of recreational use will probably increase use in the long run but the magnitude and timing of any increase is uncertain. It will be critical to monitor: cannabis use in household and high school surveys; cannabis sales; the number of cannabis plants legally produced; and the THC content of cannabis. Indicators of cannabis-related harms that should be monitored include: car crash fatalities and injuries; emergency department presentations; presentations to addiction treatment services; and the prevalence of regular cannabis use among young people in mental health services and the criminal justice system.

Plausible effects of legalizing recreational cannabis use in the USA include substantially reducing the price of cannabis and increasing heavy use and some types of cannabis-related harm among existing users. In the longer term it may also increase the number of new users.

Innovations In Clinical Neuroscience • April 2016

WHY NOT POT?: A Review of the Brain-based Risks of Cannabis

MacDonald K1, Pappas K1.

Dr. MacDonald and Ms. Pappas are with UC San Diego Psychiatry, San Diego, CA, USA

Full text with 87 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4911936/>

In this review, we provide a historical perspective on marijuana, and survey contemporary research investigating its potential negative effects on the brain. We discuss the evidence regarding cannabis dependence, driving under the influence of cannabis, underachievement, inducing (or worsening) certain psychiatric conditions, and the potential for progression to use of more dangerous drugs—summarized by the acronym DDUMB, a cognitive tool that may help healthcare providers in their risk/benefit discussions with patients who use cannabis. We also review and discuss the impact of marijuana use on target populations, including adolescents (who are at increased risk of harm); heavy users; and people suffering from-or at high risk of- mental illness. While cannabis presents certain subjective, healthrelated, and pecuniary benefits to users, growers, and other entities, it is also associated with several brainbased risks. Understanding these risks aids clinicians and their patients in making informed and balanced decisions regarding the initiation or continuance of marijuana use.

New Zealand Medical Journal • April 2016

New Zealand Health Survey 2012/13: characteristics of medicinal cannabis users

Pledger M1, Martin G, Cumming J.

Health Services Research Centre, School of Government, Victoria University of Wellington, PO Box 600, Wellington 6140
Megan.Pledger@vuw.ac.nz

<http://www.ncbi.nlm.nih.gov/pubmed/27349158>

To explore the characteristics of medicinal and non-medicinal cannabis users, and the conditions that were treated with cannabis.

About five percent (4.6%, 95% CI 4.1-5.1) of those aged 15+ report using cannabis medicinally. This use was associated with being male, younger, less well-educated and relatively poor. While Māori have the highest prevalence of medicinal use, European NZ/Others make up 67.9% (95% CI 62.7-72.6) of medicinal users. Reported medicinal use was associated with reported conditions that were typically hard to manage: pain, anxiety/nerves and depression. Medicinal users were more likely to report chronic pain and pain interfering, moderately or more, with housework and other work.

At the Tip of an Iceberg: Prenatal Marijuana and Its Possible Relation to Neuropsychiatric Outcome in the Offspring

Alpár A1, Di Marzo V2, Harkany T3.

1. MTA-SE NAP B Research Group of Experimental Neuroanatomy and Developmental Biology, Hungarian Academy of Sciences, Budapest, Hungary
Department of Anatomy, Semmelweis University, Budapest, Hungary
2. Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli, Naples, Italy
3. Division of Molecular Neurosciences, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden
Department of Molecular Neurosciences, Center for Brain Research, Medical University of Vienna, Vienna, Austria
Electronic address: Tibor.Harkany@meduniwien.ac.at

<http://www.ncbi.nlm.nih.gov/pubmed/26549491>

Endocannabinoids regulate brain development via modulating neural proliferation, migration, and the differentiation of lineage-committed cells. In the fetal nervous system, (endo)cannabinoid-sensing receptors and the enzymatic machinery of endocannabinoid metabolism exhibit a cellular distribution map different from that in the adult, implying distinct functions.

Notably, cannabinoid receptors serve as molecular targets for the psychotropic plant-derived cannabis constituent $\Delta(9)$ -tetrahydrocannabinol, as well as synthetic derivatives (designer drugs).

Over 180 million people use cannabis for recreational or medical purposes globally.

Recreational cannabis is recognized as a niche drug for adolescents and young adults.

This review combines data from human and experimental studies to show that long-term and heavy cannabis use during pregnancy can impair brain maturation and predispose the offspring to neurodevelopmental disorders. By discussing the mechanisms of cannabinoid receptor-mediated signaling events at critical stages of fetal brain development, we organize histopathologic, biochemical, molecular, and behavioral findings into a logical hypothesis predicting neuronal vulnerability to and attenuated adaptation toward environmental challenges (stress, drug exposure, medication) in children affected by in utero cannabinoid exposure. Conversely, we suggest that endocannabinoid signaling can be an appealing druggable target to dampen neuronal activity if pre-existing pathologies associate with circuit hyperexcitability. Yet, we warn that the lack of critical data from longitudinal follow-up studies precludes valid conclusions on possible delayed and adverse side effects. Overall, our conclusion weighs in on the ongoing public debate on cannabis legalization, particularly in medical contexts.

The Pharmacological Basis of Cannabis Therapy for Epilepsy

Reddy DS1, Golub VM2.

1,2. Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center, Bryan, Texas
reddy@medicine.tamhsc.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26787773>

Recently, cannabis has been suggested as a potential alternative therapy for refractory epilepsy, which affects 30% of epilepsy, both adults and children, who do not respond to current medications. There is a large unmet medical need for new antiepileptics that would not interfere with normal function in patients with refractory epilepsy and conditions associated with refractory seizures. The two chief cannabinoids are Δ -9-tetrahydrocannabinol, the major psychoactive component of marijuana, and cannabidiol (CBD), the major nonpsychoactive component of marijuana. Claims of clinical efficacy in epilepsy of CBD-predominant cannabis or medical marijuana come mostly from limited studies, surveys, or case reports. However, the mechanisms underlying the antiepileptic efficacy of cannabis remain unclear. This article highlights the pharmacological basis of cannabis therapy, with an emphasis on the endocannabinoid mechanisms underlying the emerging neurotherapeutics of CBD in epilepsy. CBD is anticonvulsant, but it has a low affinity for the cannabinoid receptors CB1 and CB2; therefore the exact mechanism by which it affects seizures remains poorly understood. A rigorous clinical evaluation of pharmaceutical CBD products is needed to establish the safety and efficacy of their use in the treatment of epilepsy. Identification of mechanisms underlying the anticonvulsant efficacy of CBD is also critical for identifying other potential treatment options.

Book Review • April 2016

Cannabis and Cannabinoids (PDQ®): Patient Version

Authors

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board

Source

PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US)

Full text, extensive resources with numerous links

<http://www.ncbi.nlm.nih.gov/books/NBK65875/>

Excerpt

This PDQ cancer information summary has current information about the use of Cannabis and cannabinoids in the treatment of people with cancer. It is meant to inform and help patients, families, and caregivers. It does not give formal guidelines or recommendations for making decisions about health care. Editorial Boards write the PDQ cancer information summaries and keep them up to date. These Boards are made up of experts in cancer treatment and other specialties related to cancer. The summaries are reviewed regularly and changes are made when there is new information. The date on each summary (“Date Last Modified”) is the date of the most recent change. The information in this patient summary was taken from the health professional version, which is reviewed regularly and updated as needed, by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board.

Book Review • April 2016

Cannabis and Cannabinoids (PDQ®): Health Professional Version

Authors

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board

Source

PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US)

Extensive resources, full text with numerous links

<http://www.ncbi.nlm.nih.gov/books/NBK65755/>

Excerpt

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of Cannabis and cannabinoids in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions. This summary is reviewed regularly and updated as necessary by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

ENDOCANNABINOID SYSTEM: A multi-facet therapeutic target

Kaur R1, Ambwani SR, Singh S.

Department of Pharmacology, AllMS, Jodhpur, Rajasthan
sidhurimple@yahoo.com

<http://www.ncbi.nlm.nih.gov/pubmed/27086601>

Cannabis sativa is also popularly known as marijuana. It is being cultivated and used by man for recreational and medicinal purposes from many centuries. Study of cannabinoids was at bay for very long time and its therapeutic value could not be adequately harnessed due to its legal status as proscribed drug in most of the countries. The research of drugs acting on endocannabinoid system has seen many ups and down in recent past. Presently, it is known that endocannabinoids has role in pathology of many disorders and they also serve “protective role” in many medical conditions. Several diseases like emesis, pain, inflammation, multiple sclerosis, anorexia, epilepsy, glaucoma, schizophrenia, cardiovascular disorders, cancer, obesity, metabolic syndrome related diseases, Parkinson’s disease, Huntington’s disease, Alzheimer’s disease and Tourette’s syndrome could possibly be treated by drugs modulating endocannabinoid system. Presently, cannabinoid receptor agonists like nabilone and dronabinol are used for reducing the chemotherapy induced vomiting. Sativex (cannabidiol and THC combination) is approved in the UK, Spain and New Zealand to treat spasticity due to multiple sclerosis. In US it is under investigation for cancer pain, another drug Epidiolex (cannabidiol) is also under investigation in US for childhood seizures. Rimonabant, CB1 receptor antagonist appeared as a promising anti-obesity drug during clinical trials but it also exhibited remarkable psychiatric side effect profile. Due to which the US Food and Drug Administration did not approve Rimonabant in US. Its sale was also suspended across the EU in 2008. Recent discontinuation of clinical trial related to FAAH inhibitor due to occurrence of serious adverse events in the participating subjects could be discouraging for the research fraternity. Despite of some mishaps in clinical trials related to drugs acting on endocannabinoid system, still lot of research is being carried out to explore and establish the therapeutic targets for both cannabinoid receptor agonists and antagonists. One challenge is to develop drugs that target only cannabinoid receptors in a particular tissue and another is to invent drugs that acts selectively on cannabinoid receptors located outside the blood brain barrier. Besides this, development of the suitable dosage forms with maximum efficacy and minimum adverse effects is also warranted. Another angle to be introspected for therapeutic abilities of this group of drugs is non-CB1 and non-CB2 receptor targets for cannabinoids. In order to successfully exploit the therapeutic potential of endocannabinoid system, it is imperative to further characterize the endocannabinoid system in terms of identification of the exact cellular location of cannabinoid receptors and their role as “protective” and “disease inducing substance”, time-dependent changes in the expression of cannabinoid receptors.

Smoking, vaping, eating: Is legalization impacting the way people use cannabis?

Borodovsky JT1, Crosier BS2, Lee DC2, Sargent JD3, Budney AJ2.

1,2. Geisel School of Medicine at Dartmouth, 46 Centerra Parkway, Lebanon, NH 03766, USA

3. C. Everett Koop Institute, Dartmouth-Hitchcock Norris Cotton Cancer Center, One Medical Center Drive, Lebanon, NH 03756, USA

Electronic address: Jacob.t.borodovsky.gr@dartmouth.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26992484>

In the context of the shifting legal landscape of medical cannabis, different methods of cannabis administration have important public health implications. How medical marijuana laws (MML) may influence patterns of use of alternative methods of cannabis administration (vaping and edibles) compared to traditional methods (smoking) is unclear. The purpose of this study was to determine if the prevalence of use of alternative methods of cannabis administration varied in relation to the presence of and variation in MMLs among states in the United States.

Using Qualtrics and Facebook, we collected survey data from a convenience sample of n=2,838 individuals who had used cannabis at least once in their lifetime. Using multiple sources, U.S. states were coded by MML status, duration of MML status, and cannabis dispensary density. Adjusted logistic and linear regression analyses were used to analyze outcomes of ever use, preference for, and age of initiation of smoking, vaping, and edibles in relation to MML status, duration of MML status, and cannabis dispensary density.

Individuals in MML states had a significantly higher likelihood of ever use of vaping (OR: 2.04, 99% CI: 1.62-2.58) and edibles (OR: 1.78, 99% CI: 1.39-2.26) than those in states without MMLs. Longer duration of MML status and higher dispensary density were also significantly associated with ever use of vaping and edibles.

MMLs are related to state-level patterns of utilization of alternative methods of cannabis administration. Whether discrepancies in MML legislation are causally related to these findings will require further study. If MMLs do impact methods of use, regulatory bodies considering medical or recreational legalization should be aware of the potential impact this may have on cannabis users.

**Genome-wide association study of lifetime cannabis use
based on a large meta-analytic sample of 32,330 subjects from the International Cannabis Consortium**

52 authors from 8 countries representing 52 different medical research institutions

Full text with 71 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4872459/>

Cannabis is the most widely produced and consumed illicit psychoactive substance worldwide. Occasional cannabis use can progress to frequent use, abuse and dependence with all known adverse physical, psychological and social consequences. Individual differences in cannabis initiation are heritable (40-48%). The International Cannabis Consortium was established with the aim to identify genetic risk variants of cannabis use. We conducted a meta-analysis of genome-wide association data of 13 cohorts (N=32 330) and four replication samples (N=5627). In addition, we performed a gene-based test of association, estimated single-nucleotide polymorphism (SNP)-based heritability and explored the genetic correlation between lifetime cannabis use and cigarette use using LD score regression. No individual SNPs reached genome-wide significance. Nonetheless, gene-based tests identified four genes significantly associated with lifetime cannabis use: NCAM1, CADM2, SCOC and KCNT2. Previous studies reported associations of NCAM1 with cigarette smoking and other substance use, and those of CADM2 with body mass index, processing speed and autism disorders, which are phenotypes previously reported to be associated with cannabis use. Furthermore, we showed that, combined across the genome, all common SNPs explained 13-20% ($P < 0.001$) of the liability of lifetime cannabis use. Finally, there was a strong genetic correlation ($r_g = 0.83$; $P = 1.85 \times 10^{-8}$) between lifetime cannabis use and lifetime cigarette smoking implying that the SNP effect sizes of the two traits are highly correlated. This is the largest meta-analysis of cannabis GWA studies to date, revealing important new insights into the genetic pathways of lifetime cannabis use. Future functional studies should explore the impact of the identified genes on the biological mechanisms of cannabis use.

Use of Embryos Extracted from Individual *Cannabis sativa* Seeds for Genetic Studies and Forensic Applications

Soler S1, Borràs D1, Vilanova S1, Sifres A1, Andújar I1, Figàs MR1, Llosa ER2, Prohens J1.

1. Institut de Conservació i Millora de l'Agrodiversitat Valenciana, Universitat Politècnica de València, Camí de Vera 14, València, 46022, Spain
2. Hemp Trading, S.L.U., Camí del Polio 51, Beniparrell, 46469, Spain

<http://www.ncbi.nlm.nih.gov/pubmed/27404624>

Legal limits on the psychoactive tetrahydrocannabinol (THC) content in *Cannabis sativa* plants have complicated genetic and forensic studies in this species. However, *Cannabis* seeds present very low THC levels. We developed a method for embryo extraction from seeds and an improved protocol for DNA extraction and tested this method in four hemp and six marijuana varieties. This embryo extraction method enabled the recovery of diploid embryos from individual seeds. An improved DNA extraction protocol (CTAB3) was used to obtain DNA from individual embryos at a concentration and quality similar to DNA extracted from leaves. DNA extracted from embryos was used for SSR molecular characterization in individuals from the 10 varieties. A unique molecular profile for each individual was obtained, and a clear differentiation between hemp and marijuana varieties was observed. The combined embryo extraction-DNA extraction methodology and the new highly polymorphic SSR markers facilitate genetic and forensic studies in *Cannabis*.

Cannabidiol protects an in vitro model of the blood-brain barrier from oxygen-glucose deprivation via PPAR γ and 5-HT $_{1A}$ receptors

Hind WH1, England TJ1, O'Sullivan SE1.

1. School of Medicine, University of Nottingham, Royal Derby Hospital, Derby, UK

<http://www.ncbi.nlm.nih.gov/pubmed/26497782>

In vivo and in vitro studies have demonstrated a protective effect of cannabidiol (CBD) in reducing infarct size in stroke models and against epithelial barrier damage in numerous disease models. We aimed to investigate whether CBD also affects blood-brain barrier (BBB) permeability following ischaemia.

Human brain microvascular endothelial cell (HBMEC) and human astrocyte co-cultures modelled the BBB. Ischaemia was modelled by oxygen-glucose deprivation (OGD) and permeability was measured by transepithelial electrical resistance.

CBD (10 μ M) prevented the increase in permeability caused by 4 h OGD. CBD was most effective when administered before the OGD, but protective effects were observed up to 2 h into reperfusion. This protective effect was inhibited by a PPAR γ antagonist and partly reduced by a 5-HT $_{1A}$ receptor antagonist, but was unaffected by antagonists of cannabinoid CB $_1$ or CB $_2$ receptors, TRPV $_1$ channels or adenosine A $_2A$ receptors. CBD also reduced cell damage, as measured by LDH release and by markers of cellular adhesion, such as the adhesion molecule VCAM-1. In HBMEC monocultures, CBD decreased VCAM-1 and increased VEGF levels, effects which were inhibited by PPAR γ antagonism.

These data suggest that preventing permeability changes at the BBB could represent an as yet unrecognized mechanism of CBD-induced neuroprotection in ischaemic stroke, a mechanism mediated by activation of PPAR γ and 5-HT $_{1A}$ receptors.

The Journal Of Law In Medicine • March 2016

MEDICINAL CANNABIS LAW REFORM IN AUSTRALIA

By I. Freckelton

<http://www.ncbi.nlm.nih.gov/pubmed/27323630>

Attempts at medicinal cannabis law reform in Australia are not new. However, in historical perspective 2015 and 2016 will be seen as the time when community debate about legalisation of medicinal cannabis reached a tipping point in a number of Australian jurisdictions and when community impetus for change resulted in major reform initiatives. In order to contextualise the changes, the August 2015 Report of the Victorian Law Reform Commission (VLRC) and then the Access to Medicinal Cannabis Bill 2015 (Vic) introduced in December 2015 into the Victorian Parliament by the Labor Government are scrutinised. In addition, this editorial reviews the next phase of developments in the course of 2015 and 2016, including the Commonwealth Narcotic Drugs Amendment Act 2016 and the Queensland Public Health (Medicinal Cannabis) Bill 2016. It identifies the principal features of the legislative initiatives against the backdrop of the VLRC proposals. It observes that the principles underlying the Report and the legislative developments in the three Australian jurisdictions are closely aligned and that their public health approach, their combination of evidence-based pragmatism, and their carefully orchestrated checks and balances against abuse and excess constitute a constructive template for medicinal cannabis law reform.

Integrating cannabis into clinical cancer care

Abrams DI1.

Hematology-Oncology, San Francisco General Hospital
Integrative Oncology, UCSF Osher Center for Integrative Medicine
and University of California-San Francisco, San Francisco, CA, USA

Full text with 58 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791148/>

Cannabis species have been used as medicine for thousands of years; only since the 1940s has the plant not been widely available for medical use. However, an increasing number of jurisdictions are making it possible for patients to obtain the botanical for medicinal use. For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combatting anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression.

Cannabis might be less potent than other available antiemetics, but for some patients, it is the only agent that works, and it is the only antiemetic that also increases appetite. Inhaled cannabis is more effective than placebo in ameliorating peripheral neuropathy in a number of conditions, and it could prove useful in chemotherapy-induced neuropathy.

A pharmacokinetic interaction study of vaporized cannabis in patients with chronic pain on stable doses of sustained-release opioids demonstrated no clinically significant change in plasma opiates, while suggesting the possibility of synergistic analgesia. Aside from symptom management, an increasing body of in vitro and animal-model studies supports a possible direct anticancer effect of cannabinoids by way of a number of different mechanisms involving apoptosis, angiogenesis, and inhibition of metastasis.

Despite an absence of clinical trials, abundant anecdotal reports that describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate, are circulating. Human studies should be conducted to address critical questions related to the foregoing effects.

Current Oncology • March 2016

Why I chose to use cannabis

By L. Perrier • Ovarian cancer patient, Montreal, QC.

Correspondence to: Louise Perrier, 5206 Hingston Avenue, Montreal, Quebec H3X 3R4

E-mail: moc.setaicossareirrep@reirrep.esiuoL

Full text

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791147/>

I just learned that my ovarian cancer is back and that I need to start chemotherapy. At 5 feet, 7 inches, I weigh only 95 pounds, having lost 30 pounds since the surgery. I don't want to lose any more weight. And so I research options to help with appetite. All recommended products have side effects I don't like. The one exception is cannabis. I decide to ask my oncologist for a prescription. From my perspective, cannabis has made a large impact on my quality of life. I am very happy I jumped through a bunch of hoops to get it.

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Devinsky O1, Marsh E2, Friedman D3, Thiele E4, Laux L5, Sullivan J6, Miller I7, Flamini R8, Wilfong A9, Filloux F10, Wong M11, Tilton N6, Bruno P4, Bluvstein J3, Hedlund J3, Kamens R2, Maclean J2, Nangia S5, Singhal NS6, Wilson CA10, Patel A12, Cilio MR6.

1. Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, NY, USA
 2. Departments of Neurology and Pediatrics, Division of Child Neurology, Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
 3. Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, NY, USA
 4. Massachusetts General Hospital for Children, Boston, MA, USA
 5. Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA
 6. Departments of Neurology and Pediatrics, Benioff Children's Hospital, University of California, San Francisco, San Francisco, CA, USA
 7. Miami Children's Hospital, Miami, FL, USA
 8. Pediatric and Adolescent Neurodevelopmental Associates, Atlanta, GA, USA
 9. Texas Children's Hospital, Houston, TX, USA
 10. University of Utah Medical Center and Primary Children's Hospital, Salt Lake City, UT, USA
 11. Wake Forest School of Medicine, Winston-Salem, NC, USA
 12. Nationwide Children's Hospital, Columbus, OH, USA
- Electronic address: od4@nyu.edu

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<http://www.ncbi.nlm.nih.gov/pubmed/26724101>

Almost a third of patients with epilepsy have a treatment-resistant form, which is associated with severe morbidity and increased mortality. Cannabis-based treatments for epilepsy have generated much interest, but scientific data are scarce. We aimed to establish whether addition of cannabidiol to existing anti-epileptic regimens would be safe, tolerated, and efficacious in children and young adults with treatment-resistant epilepsy.

Our findings suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy. Randomised controlled trials are warranted to characterise the safety profile and true efficacy of this compound.

Current Oncology • March 2016

Cannabis and cancer: toward a new understanding

M.A. Ware, MBBS MSc

Anesthesia and Family Medicine, McGill University, and the Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, QC

Correspondence to: Mark A. Ware, A5.140 Montreal General Hospital, 1650 Cedar Avenue, Montreal H3G 1A4

E-mail: ac.ligcm@eraw.kram

Full text

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791146/>

The treatment of cancer, including the disease itself and the symptoms associated with cancer and its therapy, is one of the most important emerging frontiers in cannabinoid therapeutics. With new regulatory environments opening up in Canada and around the world, access to a variety of quality-controlled cannabis-based products and administration techniques is becoming a reality for patients and their families desperate for new approaches to the devastating effects of cancer. The same is true for scientists and clinical researchers, who are starting to realize that, after years of deep freeze on cannabis-related research, funding, and materials, a thaw is starting. The promise, and even the hype, can reach hysterical proportions, with claims of cannabis cancer cures circulating in cyberspace at a furious pace. The challenge in the coming months and years will be to channel this interest into a productive clinical research program that informs and enlightens all those affected by cancer and its ravages.

Crude estimates of cannabis-attributable mortality and morbidity in Canada— implications for public health focused intervention priorities

Fischer B1, Imtiaz S2, Rudzinski K3, Rehm J4.

1. Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Canada
Centre for Applied Research in Mental Health and Addiction, Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada
Department of Psychiatry, University of Toronto, Toronto, Canada
2. Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Canada
Institute of Medical Science, University of Toronto, Toronto, Canada
3. Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Canada
Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
4. Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Canada
Department of Psychiatry, University of Toronto, Toronto, Canada
Institute of Medical Science, University of Toronto, Toronto, Canada
Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
WHO/PAHO Collaborating Centre for Mental Health and Addiction, Toronto, Canada
Klinische Psychologie und Psychotherapie, Technische Universität Dresden, Dresden 01069, Germany

<http://www.ncbi.nlm.nih.gov/pubmed/25630540>

Cannabis is the most commonly used drug in Canada; while its use is currently controlled by criminal prohibition, debates about potential control reforms are intensifying. There is substantive evidence about cannabis-related risks to health in various key outcome domains; however, little is known about the actual extent of these harms specifically in Canada.

Motor Vehicle Accidents and lung cancer are the only domains where cannabis-attributable mortality is estimated to occur. While cannabis use results in morbidity in all domains, MVAs and use disorders by far outweigh the other domains in the number of cases; the popularly debated mental health consequences (e.g., psychosis) translate into relatively small case numbers.

The present crude estimates should guide and help prioritize public health-oriented interventions for the cannabis-related health burden in the population in Canada; formal burden of disease calculations should be conducted.

In vitro and in vivo efficacy of non-psychoactive cannabidiol in neuroblastoma

Fisher T1, Golan H2, Schiby G3, PriChen S4, Smoum R5, Moshe I1, Peshes-Yaloz N6, Castiel A6, Waldman D2, Gallily R7, Mechoulam R5, Toren A8.

1. Pediatric Hemato-Oncology Research Laboratory, Sheba Cancer Research Center
2. Pediatric Hemato-Oncology Research Laboratory, Sheba Cancer Research Center
Department of Pediatric Hemato-Oncology, The Edmond and Lily Safra Children's Hospital
3. Department of Pathology, The Chaim Sheba Medical Center, Tel-Hashomer, Israel
4. Pediatric Stem Cell Research Institute, The Chaim Sheba Medical Center, Tel-Hashomer, Israel
5. Institute for Drug Research, Hebrew University of Jerusalem, Jerusalem, Israel
6. Cancer Research Center, The Chaim Sheba Medical Center, Tel-Hashomer, Israel
7. The Lautenberg Center for General and Tumour Immunology, Hebrew University of Jerusalem, Jerusalem, Israel
8. Department of Pediatric Hemato-Oncology, The Edmond and Lily Safra Children's Hospital; Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Full text with 50 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791143/>

Neuroblastoma (nbl) is one of the most common solid cancers in children. Prognosis in advanced nbl is still poor despite aggressive multimodality therapy. Furthermore, survivors experience severe long-term multi-organ sequelae. Hence, the identification of new therapeutic strategies is of utmost importance. Cannabinoids and their derivatives have been used for years in folk medicine and later in the field of palliative care. Recently, they were found to show pharmacologic activity in cancer, including cytostatic, apoptotic, and antiangiogenic effects.

Both compounds have antitumorigenic activity in vitro and impeded the growth of tumour xenografts in vivo. Of the two cannabinoids tested, cbd was the more active. Treatment with cbd reduced the viability and invasiveness of treated tumour cells in vitro and induced apoptosis (as demonstrated by morphology changes, sub-G1 cell accumulation, and annexin V assay). Moreover, cbd elicited an increase in activated caspase 3 in treated cells and tumour xenografts.

Our results demonstrate the antitumorigenic action of cbd on nbl cells. Because cbd is a nonpsychoactive cannabinoid that appears to be devoid of side effects, our results support its exploitation as an effective anticancer drug in the management of nbl.

Abnormal medial prefrontal cortex activity in heavy cannabis users during conscious emotional evaluation

Wesley MJ1, Lile JA2, Hanlon CA3, Porrino LJ4.

1,2. Department of Behavioral Science, University of Kentucky College of Medicine, Medical Behavioral Science Building, Lexington, KY, USA

3. Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

4. Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC, USA

michael.wesley@uky.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26690589>

Long-term heavy cannabis users who are not acutely intoxicated have diminished subconscious neural responsiveness to affective stimuli.

This study sought to determine if abnormal processing extends to the conscious evaluation of emotional stimuli.

Functional magnetic resonance imaging (fMRI) was used to examine brain activity as cannabis users (N = 16) and non-cannabis-using controls (N = 17) evaluated and categorized standardized International Affective Picture System (IAPS) stimuli. Individual judgments were used to isolate activity during the evaluation of emotional (i.e., emotional evaluation) or neutral (i.e., neutral evaluation) stimuli. Within- and between-group analyses were performed.

Both groups judged the same stimuli as emotional and had activations in visual, midbrain, and middle cingulate cortices during emotional evaluation, relative to neutral. Within-group analyses also revealed amygdalar and inferior frontal gyrus activations in controls, but not cannabis users, and medial prefrontal cortex (mPFC) deactivations in cannabis users, but not controls, during emotional evaluation, relative to neutral. Between-group comparisons found that mPFC activity during positive and negative evaluation was significantly hypoactive in cannabis users, relative to controls.

Abnormal neural processing of affective content extends to the level of consciousness in cannabis users. The hypoactive mPFC responses observed resembles the attenuated mPFC responses found during increased non-affective cognitive load in prior research. These findings suggest that abnormal mPFC signaling in cannabis users during emotional evaluation might be associated with increased non-affective cognitive load.

Endocannabinoids—at the crossroads between the gut microbiota and host metabolism

Cani PD1, Plovier H1, Van Hul M1, Geurts L1, Delzenne NM2, Druart C1, Everard A1.

1. Walloon Excellence in Life Sciences and BIOtechnology (WELBIO), Metabolism and Nutrition Research Group
Louvain Drug Research Institute, Université catholique de Louvain, Avenue E. Mounier 73, Box B1.73.11, Brussels B-1200, Belgium
2. Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université
catholique de Louvain, Avenue E. Mounier 73, Box B1.73.11, Brussels B-1200, Belgium

<http://www.ncbi.nlm.nih.gov/pubmed/26678807>

Various metabolic disorders are associated with changes in inflammatory tone. Among the latest advances in the metabolism field, the discovery that gut microorganisms have a major role in host metabolism has revealed the possibility of a plethora of associations between gut bacteria and numerous diseases. However, to date, few mechanisms have been clearly established. Accumulating evidence indicates that the endocannabinoid system and related bioactive lipids strongly contribute to several physiological processes and are a characteristic of obesity, type 2 diabetes mellitus and inflammation. In this Review, we briefly define the gut microbiota as well as the endocannabinoid system and associated bioactive lipids. We discuss existing literature regarding interactions between gut microorganisms and the endocannabinoid system, focusing specifically on the triad of adipose tissue, gut bacteria and the endocannabinoid system in the context of obesity and the development of fat mass. We highlight gut-barrier function by discussing the role of specific factors considered to be putative 'gate keepers' or 'gate openers', and their role in the gut microbiota-endocannabinoid system axis. Finally, we briefly discuss data related to the different pharmacological strategies currently used to target the endocannabinoid system, in the context of cardiometabolic disorders and intestinal inflammation.

Excess Mortality from Mental, Neurological, and Substance Use Disorders in the Global Burden of Disease Study 2010

Authors

Charlson FJ, Baxter AJ, Dua T, Degenhardt L, Whiteford HA, Vos T.

Editors

Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME.

<http://www.ncbi.nlm.nih.gov/pubmed/27227239>

Excerpt

Findings from the Global Burden of Disease Study 2010 (GBD 2010) have reinforced the understanding of the significant impact that mental, neurological, and substance use disorders have on population health (Murray and others 2012; Whiteford and others 2013). One key finding was the health transition from communicable to noncommunicable diseases across all regions. This transition was particularly evident in low- and middle-income countries (LMICs) (Murray and others 2012), where the proportion of burden attributable to noncommunicable disease increased from 36 percent in 1990 to 49 percent in 2010, compared with an increase from 80 percent to 83 percent in high-income countries (HICs) (IHME 2013). GBD 2010 estimates that the majority of disease burden caused by mental, neurological, and substance use disorders is from nonfatal health loss; only 15 percent of the total burden is from mortality in years of life lost (YLLs) (IHME 2013). This finding may erroneously lead to the interpretation that premature death in people with mental, neurological, and substance use disorders is inconsequential. A recent review has shown higher mortality risks than the general population for a range of mental disorders, with a standardized mortality ratio (SMR) as high as 14.7 for opioid use disorders (Chesney, Goodwin, and Fazel 2014). Excess mortality in people with epilepsy is reported to be two-to three-fold higher than that of the general population, with an increased risk up to six-fold higher in LMICs (Diop and others 2005). A

significant proportion of these deaths is preventable (Diop and others 2005; Jette and Trevathan 2014). There are multiple causes for lower life expectancy in people with mental disorders (Chang and others 2011; Crump and others 2013; Lawrence, Hancock, and Kisely 2013). Self-harm is an important cause of death, but the majority of premature deaths are caused by chronic physical disease, particularly ischemic heart disease (IHD), stroke, type II diabetes, respiratory diseases, and cancer (Crump and others 2013; Lawrence, Hancock, and Kisely 2013). Dementia is an independent risk factor for premature death; and patients with physical impairment, inactivity, and medical comorbidities are at increased risk (Park and others 2014). In many HICs, the life expectancy gap between those with mental disorders and the general population is widening. The general population enjoys a longer life, while the lifespan for those with mental, neurological, and substance use disorders remains significantly lower and unchanged (Lawrence, Hancock, and Kisely 2013). Information on the extent and causes of premature mortality in people with mental, neurological, and substance use disorders in LMICs is sparse, but these groups are understood to experience reduced life expectancy, although causes of death may vary across regions. This chapter explores the cause-specific and excess mortality of individual mental, neurological, and substance use disorders estimated by GBD 2010 and discusses the results. We present the additional burden that

can be attributed to these disorders, using GBD results for comparative risk assessments (CRAs) assessing mental, neurological, and substance use disorders as risk factors for other health outcomes. We focus on the following mental, neurological, and substance use disorders: Mental disorders, including schizophrenia, major depressive disorder, anxiety disorders, bipolar disorder, autistic disorder, and disruptive behavioral disorders (attention-deficit hyperactivity disorder [ADHD] and conduct disorder [CD]). Substance use disorders, including alcohol use disorders (alcohol dependence and fetal alcohol syndrome) and opioid, cocaine, cannabis, and amphetamine dependence. Neurological disorders, including dementia, epilepsy, and migraine. For the purposes of GBD 2010, countries were grouped into 21 regions and 7 super-regions based on geographic proximity and levels of child and adult mortality (IHME 2014; Murray and others 2012). Regions were further grouped into developed and developing categories using the GBD 2010 method. Details of countries in each region and super-region can be found on the Institute for Health Metrics and Evaluation (IHME) website (IHME 2014). The mortality associated with a disease can be quantified using two different, yet complementary, methods employed as part of the GBD analyses. First, cause-specific mortality draws on vital registration systems and verbal autopsy studies that identify deaths attributed to a single underlying cause using the International Classification of Diseases (ICD) death coding system. Second, GBD creates natural history models of disease, drawing on a range of epidemiological inputs, which ultimately provide epidemiological estimates for parameters including excess mortality—that is, the all-cause mortality

rate in a population with the disorder above the all-cause mortality rate observed in a population without the disorder. By definition, the estimates of excess deaths include cause-specific deaths. Although arbitrary, the ICD conventions are a necessary attempt to deal with the multi-causal nature of mortality and avoid the double-counting of deaths. Despite the system's clear strengths, cause-specific mortality estimated via the ICD obscures the contribution of other underlying causes of death—for example, suicide as a direct result of major depressive disorder—and likely underestimates the true number of deaths attributable to a particular disorder. However, the estimation of excess mortality using natural history models often includes deaths from causal and noncausal origins and likely overestimates the true number of deaths attributable to a particular disorder. The challenge is to parse out causal contributions to mortality, beyond those already identified as cause-specific, from the effects of confounders. The quantification of the burden attributable to risk factors requires approaches such as CRA, which is now an integral part of the GBD studies. The fundamental approach is to calculate the proportion of deaths or disease burden caused by specific risk factors—for example, lung cancer caused by tobacco smoking—while holding all other independent factors constant. A counterfactual approach is used to compare the burden associated to an outcome with the amount expected in a hypothetical situation of ideal risk factor exposure, for example, zero prevalence. This provides a consistent method for estimating the changes in population health when decreasing or increasing the level of exposure to risk factors (Lim and others 2012).

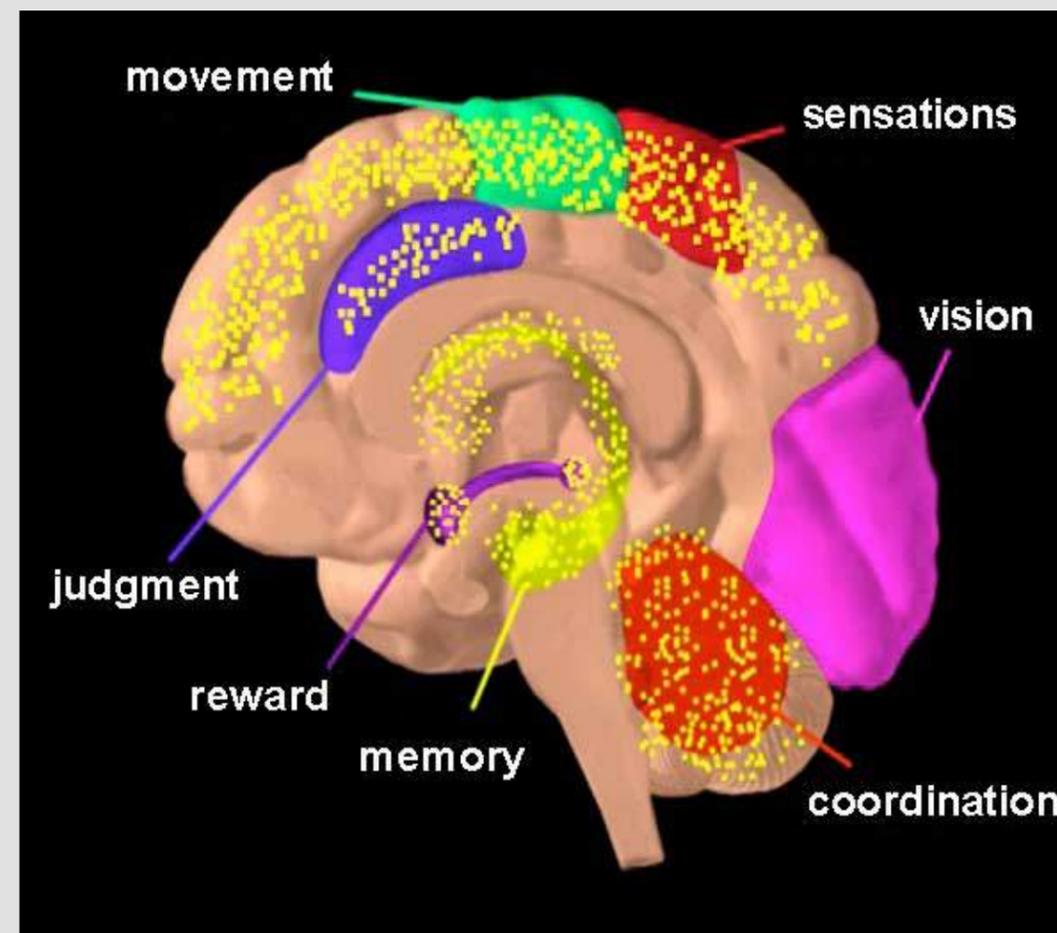
DrugFacts: Marijuana

Full text with 10 references

<https://www.drugabuse.gov/publications/drugfacts/marijuana>

Marijuana also affects brain development. When marijuana users begin using as teenagers, the drug may reduce thinking, memory, and learning functions and affect how the brain builds connections between the areas necessary for these functions. Marijuana's effects on these abilities may last a long time or even be permanent. For example, a study showed that people who started smoking marijuana heavily in their teens and had an ongoing cannabis use disorder lost an average of eight IQ points between ages 13 and 38. The lost mental abilities did not fully return in those who quit marijuana as adults. Those who started smoking marijuana as adults did not show notable IQ declines. THC acts on numerous areas (in yellow) in the brain.

When a person smokes marijuana, THC quickly passes from the lungs into the bloodstream. The blood carries the chemical to the brain and other organs throughout the body. The body absorbs THC more slowly when the person eats or drinks it. In that case, the user generally feels the effects after 30 minutes to 1 hour. THC acts on specific brain cell receptors that ordinarily react to natural THC-like chemicals in the brain. These natural chemicals play a role in normal brain development and function. Marijuana overactivates parts of the brain that contain the highest number of these receptors. This causes the "high" that users feel. Other effects include:



- altered senses (for example, seeing brighter colors)
- altered sense of time
- changes in mood
- impaired body movement
- difficulty with thinking and problem-solving
- impaired memory

Characteristics of Child Maltreatment and Adolescent Marijuana Use: A Prospective Study

Dubowitz H1, Thompson R2, Arria AM3, English D4, Metzger R5, Kotch JB6.

1. Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA
2. Richard H. Calica Center for Innovation in Children and Family Services, Juvenile Protective Association, Chicago, IL, USA
3. Department of Behavioral and Community Health, University of Maryland School of Public Health, College Park, MD, USA
4. School of Social Work, University of Washington, Seattle, WA, USA
5. Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA
6. Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
hdubowitz@pediatrics.umaryland.edu

Full text with 88 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4713244/>

There has been increasing acceptance of marijuana use in the United States in recent years, and rates among adolescents have risen. At the same time, marijuana use during adolescence has been linked to an array of health and social problems. Maltreated children are at risk for marijuana use, but the relationships among characteristics of maltreatment and marijuana use are unclear. In this article, we examine how the type and the extent of maltreatment are related to the level of adolescent marijuana use. Data analyses were conducted on a subsample of maltreated adolescents ($n = 702$) from the Longitudinal Studies of Child Abuse and Neglect project. Approximately half the sample had used marijuana, and maltreatment was associated with its use. Multivariate regression models showed that being male, extensive maltreatment, and peer marijuana use were associated with heavy use of marijuana. These findings suggest the importance of comprehensively assessing children's maltreatment experiences and their peers' drug use to help prevent or address possible marijuana use in these high-risk adolescents.

Cannabis sativa: The Plant of the Thousand and One Molecules

Andre CM1, Hausman JF1, Guerriero G1.

Environmental Research and Innovation, Luxembourg Institute of Science and Technology Esch-sur-Alzette, Luxembourg

Full text with 169 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740396/>

Cannabis sativa L. is an important herbaceous species originating from Central Asia, which has been used in folk medicine and as a source of textile fiber since the dawn of times. This fast-growing plant has recently seen a resurgence of interest because of its multi-purpose applications: it is indeed a treasure trove of phytochemicals and a rich source of both cellulosic and woody fibers. Equally highly interested in this plant are the pharmaceutical and construction sectors, since its metabolites show potent bioactivities on human health and its outer and inner stem tissues can be used to make bioplastics and concrete-like material, respectively. In this review, the rich spectrum of hemp phytochemicals is discussed by putting a special emphasis on molecules of industrial interest, including cannabinoids, terpenes and phenolic compounds, and their biosynthetic routes. Cannabinoids represent the most studied group of compounds, mainly due to their wide range of pharmaceutical effects in humans, including psychotropic activities. The therapeutic and commercial interests of some terpenes and phenolic compounds, and in particular stilbenoids and lignans, are also highlighted in view of the most recent literature data. Biotechnological avenues to enhance the production and bioactivity of hemp secondary metabolites are proposed by discussing the power of plant genetic engineering and tissue culture. In particular two systems are reviewed, i.e., cell suspension and hairy root cultures. Additionally, an entire section is devoted to hemp trichomes, in the light of their importance as phytochemical factories. Ultimately, prospects on the benefits linked to the use of the -omics technologies, such as metabolomics and transcriptomics to speed up the identification and the large-scale production of lead agents from bioengineered *Cannabis* cell culture, are presented.

CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience

Tzadok M1, Uliel-Siboni S2, Linder I3, Kramer U2, Epstein O4, Menascu S2, Nissenkorn A5, Yosef OB5, Hyman E4, Granot D6, Dor M7, Lerman-Sagie T3, Ben-Zeev B5.

1. Pediatric Neurology Units of Chaim Sheba Medical Center, Tel Hashomer
 2. Pediatric Neurology Units of Tel Aviv Sourasky Medical Center, Tel Aviv
 3. Pediatric Neurology Units of Wolfson Medical Center, Holon
 4. Pediatric Neurology Units of Assaf Harofeh Medical Center, Zrifin
 5. Pediatric Neurology Units of Chaim Sheba Medical Center, Tel Hashomer
 6. Pediatric Neurology Units of Panaxia Medical Devices and Pharmaceuticals, Tel Aviv, Israel
 7. Pediatric Neurology Units of Medical Cannabis Unit, Ministry of Health, Tel Aviv, Israel
- Electronic address: Michal.tzadok@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/26800377>

CBD treatment yielded a significant positive effect on seizure load. Most of the children (66/74, 89%) reported reduction in seizure frequency: 13 (18%) reported 75-100% reduction, 25 (34%) reported 50-75% reduction, 9 (12%) reported 25-50% reduction, and 19 (26%) reported <25% reduction. Five (7%) patients reported aggravation of seizures which led to CBD withdrawal. In addition, we observed improvement in behavior and alertness, language, communication, motor skills and sleep. Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients.

The results of this multicenter study on CBD treatment for intractable epilepsy in a population of children and adolescents are highly promising. Further prospective, well-designed clinical trials using enriched CBD medical cannabis are warranted.

Endocannabinoids in the Gut

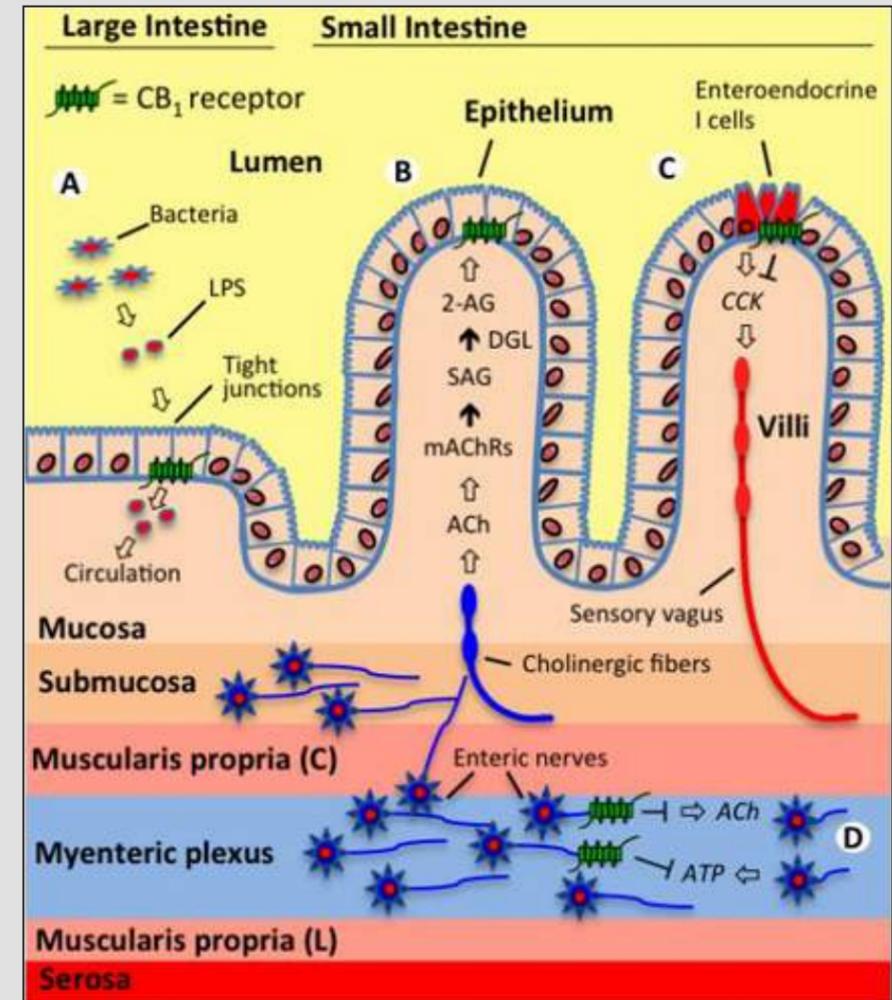
By N.V. DiPatrizio

Full text with 78 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4940133/>

Cannabis has been used medicinally for centuries to treat a variety of disorders, including those associated with the gastrointestinal tract. The discovery of our bodies' own "cannabis-like molecules" and associated receptors and metabolic machinery - collectively called the endocannabinoid system - enabled investigations into the physiological relevance for the system, and provided the field with evidence of a critical function for this endogenous signaling pathway in health and disease. Recent investigations yield insight into a significant participation for the endocannabinoid system in the normal physiology of gastrointestinal function, and its possible dysfunction in gastrointestinal pathology. Many gaps, however, remain in our understanding of the precise neural and molecular mechanisms across tissue departments that are under the regulatory control of the endocannabinoid system. This review highlights research that reveals an important - and at times surprising - role for the endocannabinoid system in the control of a variety of gastrointestinal functions, including motility, gut-brain mediated fat intake and hunger signaling, inflammation and gut permeability, and dynamic interactions with gut microbiota.

The endocannabinoid system controls a variety of gastrointestinal functions. (A) The endocannabinoid system in the large intestine is proposed to interact with gut microbiota and regulate epithelial barrier permeability. For example, activating cannabinoid 1 receptors (CB1Rs) in mice increased circulating levels of lipopolysaccharide (LPS) - which is an endotoxin released from gram-negative bacteria - through a proposed mechanism that includes decreased expression of the tight junction proteins, occludin and zonula occludens-1, and resulting increases in permeability 75. It is suggested that CB1Rs located in the intestinal epithelium control these processes. (B) Endocannabinoid signaling in the jejunum mucosa of the small intestine is triggered by fasting and tasting dietary fats, and is proposed to be a general hunger signal that acts at local CB1Rs to inhibit satiation 42,43. The evidence suggests that during fasting, cholinergic signaling (acetylcholine, ACh) - possibly by the efferent vagus nerve - activates muscarinic acetylcholine receptors (mAChRs) in the small intestine, which in turn, drives the conversion of the 2-AG precursor, 1, stearoyl,2-arachidonoyl glycerol (SAG), into 2-AG through the activity of diacylglycerol lipase (DGL). Inhibiting subtype m3 mAChRs locally in the rat intestine blocked fasting-induced production of 2-AG in the jejunum mucosa, and inhibited refeeding after a 24 h fast to the same levels as when a peripherally-restricted CB1R antagonist was administered 43. (C) Endocannabinoid activity at CB1Rs located on small intestinal enteroendocrine I cells - which produce and secrete the peptide, cholecystokinin (CCK) - are suggested to promote feeding during a fast and drive the intake of fat-rich foods by inhibiting the release of CCK, which normally binds CCK receptors on the sensory vagus nerve and induces satiation after a meal 42,43. Supporting this hypothesis, the expression of CB1R mRNA on CCK-containing enteroendocrine I cells in the mouse small intestine has been reported, 59, which suggests that CB1Rs in the gut mucosa control feeding by inhibiting the release of CCK and therefore indirectly modifying the activity of the sensory vagus. (D) Many studies provide evidence that CB1Rs on enteric nerves control intestinal contractility by inhibiting the release of the excitatory neurotransmitter, ACh 1. Recent studies also suggest that contractility is controlled by a dynamic interplay between the retrograde messengers, the endocannabinoids and purines (e.g., adenosine triphosphate, ATP), which act in an opposing manner. It is proposed that the excitatory actions on contractility for ATP are mediated through increases in ACh, which are inhibited by the activation of prejunctional CB1Rs on enteric nerves 33,34. Both systems may functionally interact to regulate synaptic strength in the enteric nervous system. Continued next page.





Fatty food intake is driven by gut-brain endocannabinoid signaling. Tasting dietary fat increases endocannabinoid levels within the rat jejunum ⁴². Inhibiting local endocannabinoid signaling at jejunal CB1Rs reduces fat intake and preferences for unsaturated dietary fats ^{42,53}. Here, a rat prefers to eat fat-rich potato chips rather than a standard laboratory chow, which contains far lower quantities of dietary fat than chips. Thus, it is proposed for illustrative purposes that this rat's preference for the fat-rich food is driven by an enhancement of gut-brain endocannabinoid signaling (i.e., the body's natural "cannabis-like molecules") that is triggered by tasting the fat contained in the chips.

Journal Of Alcohol Drug Dependency • February 2016

(–)-Trans- Δ 9-Tetrahydrocannabinol-Like Discriminative-Stimulus Effects of Gabapentin in Cannabis Users

Takato Hiranita

Full text with 42 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4930106/>

A recent study by Dr. Joshua Lile and his colleagues demonstrated the capability of gabapentin to produce marijuana-like effects in humans. The finding is unexpected since the primary binding site of gabapentin is not thought to be any of the cannabinoid receptor subtypes. Gabapentin (Neurontin®) (Figure 1) is an FDA-approved medication for the treatment of epilepsy and neuropathic pain and several cases of its off-label use are also known. Several case reports have indicated gabapentin misuse/abuse [1-4] but the in vivo pharmacology and abuse potential of gabapentin have not yet been directly characterized. Thus, there is a clear need to characterize the in vivo pharmacology of gabapentin including its abuse potential.

Cannabis—Position Paper of the German Respiratory Society (DGP)

Kreuter M1, Nowak D2, Rüter T3, Hoch E4, Thomasius R5, Vogelberg C6, Brockstedt M7, Hellmann A8, Gohlke H9, Jany B10, Loddenkemper R11.

1. Pneumologie und Beatmungsmedizin, Thoraxklinik, Universitätsklinikum Heidelberg
2. Arbeits-, Sozial- und Umweltmedizin, Klinikum der Universität München
3. Klinik für Psychiatrie und Psychotherapie, Klinikum der Universität München, Campus Innenstadt, München
4. Klinik und Poliklinik für Psychiatrie und Psychotherapie, Klinikum der Universität München, Campus Innenstadt, München
5. Deutsches Zentrum für Suchtfragen des Kindes- und Jugendalters, Universitätsklinikum Hamburg-Eppendorf
6. Klinik u. Poliklinik f. Kinder- u. Jugendmedizin, Abteilung Kinderpneumologie/Allergologie, Universitätsklinikum Carl Gustav Carus, Dresden
7. Gesundheitsamt Berlin-Mitte, Berufsverband für Kinder- und Jugendärzte
8. Zentrum für Pneumologie und Onkologie am Diako Augsburg, Bundesverband der Pneumologen, Schlaf- und Beatmungsmediziner
9. Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, Innere Medizin & Pneumologie, Missionsärztliche Klinik, Würzburg
10. Deutsche Gesellschaft für Kardiologie und Deutsche Herzstiftung
11. Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, Berlin

<http://www.ncbi.nlm.nih.gov/pubmed/26935046>

Full text in German only

<https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0042-100040>

In this position paper, the adverse health effects of cannabis are reviewed based on the existing scientific literature; in addition possible symptom-relieving effects on some diseases are depicted. In Germany, cannabis is the most widely used illicit drug. Approximately 600,000 adult persons show abusive or addictive cannabis consumption. In 12 to 17 year old adolescents, cannabis use increased from 2011 to 2014 from 2.8 to 6.4%, and the frequency of regular use from 0.2 to 1.5%. Currently, handling of cannabinoids is much debated in politics as well as in general public. Health aspects have to be incorporated into this debate. Besides analysing mental and neurological side effects, this position paper will mainly focus on the influences on the bronchopulmonary and cardiovascular system. There is strong evidence for the induction of chronic bronchitis. Allergic reactions including asthma are known, too. Associations with other diseases like pulmonary emphysema, lung cancer and pneumonia are not sufficiently proven, however cannot be excluded either. In connection with the use of cannabis cardiovascular events such as coronary syndromes, peripheral vascular diseases and cerebral complications have been noted. Often, the evidence is insufficient due to various reasons; most notably, the overlapping effects of tobacco and cannabis use can frequently not be separated adequately. Empirically, early beginning, high-dosed, long-lasting and regular cannabis consumption increase the risk of various psychological and physical impairments and negatively affect age-based development. Concerns therefore relate especially to children and adolescents. There is only little scientific evidence for medical benefits through cannabis as a remedy; systematic research of good quality, in particular prospective, randomised, placebo-controlled double-blinded studies are rare. The medical societies signing this position paper conclude that cannabis consumption is linked to adverse health effects which have to be taken into consideration in the debate about the social attitude towards cannabinoids. The societies agree that many aspects regarding health effects of cannabis are still uncertain and need clarification, preferably through research provided by controlled studies.

Review of Various Herbal Supplements as Complementary Treatments for Oral Cancer

Godsey J1, Grundmann O1.

Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, Florida, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26863913>

In the United States, nearly 44,000 people are diagnosed with oral or pharyngeal cancer annually. The life expectancy for those who are diagnosed have a survival rate of 57% after five years. Among them, oral cancer can be classified as benign or malignant tumors and is diagnosed at several stages in the development: premalignant conditions, premalignant lesions, and malignant cancer. The early signs of oral cancer often go unnoticed by the individual and are often discovered during routine dental examinations. Early detection and treatment may help to increase patient survival rates. The most widely used treatments for oral cancer include surgery, radiation, and chemotherapy-alone or in combination. Preclinical and clinical evidence for the use of green tea, raspberry, asparagus, and cannabis extracts is discussed in this review. Diet changes, supplementation with antioxidants, high-dose vitamin C therapy, and cannabinoid use have been suggested to decrease cancer cell replication and increase chance of remission. Early detection and lifestyle changes, including the use of dietary supplements in at-risk populations, are critical steps in preventing and successfully treating oral cancer. The main evidence for supplement use is currently in cancer prevention rather than treatment. Further research, determination, and mechanism of action for bioactive compounds such as epigallocatechin, epicatechin-3-gallate, and Bowman-Birk inhibitor concentrate, through in vitro, in vivo, and clinical trials need to be completed to support the use of natural products and their effectiveness in preventative care and supporting therapeutic approaches.

Cannabinoids in palliative care: Systematic review and meta-analysis of efficacy, tolerability and safety

Mücke M1,2,3, Carter C4, Cuhls H4, Prüß M5, Radbruch L4,6, Häuser W7,8.

1. Klinik für Palliativmedizin, Universitätsklinikum Bonn, Sigmund-Freud-Str. 25, 53127, Bonn, Deutschland
2. Institut für Hausarztmedizin, Medizinische Fakultät, Universität Bonn, Bonn, Deutschland
3. Zentrum für Seltene Erkrankungen (ZSEB), Universitätsklinikum Bonn, Bonn, Deutschland
4. Klinik für Palliativmedizin, Universitätsklinikum Bonn, Sigmund-Freud-Str. 25, 53127, Bonn, Deutschland
5. Charité Centrum Innere Medizin mit Gastroenterologie und Nephrologie, Universitätsmedizin Berlin, Berlin, Deutschland
6. Zentrum für Palliativmedizin, Malteser Krankenhaus Seliger Gerhard Bonn/Rhein-Sieg, Bonn, Deutschland
7. Innere Medizin I, Klinikum Saarbrücken gGmbH, Saarbrücken, Deutschland
8. Klinik für Psychosomatische Medizin und Psychotherapie, Technische Universität München, München, Deutschland
martin.muecke@ukb.uni-bonn.de

<http://www.ncbi.nlm.nih.gov/pubmed/26809975>

Cannabinoids have multiple medical indications in palliative care, such as relief of pain or nausea or increase of appetite and weight stabilisation.

Out of initially 108 studies 9, with a total of 1561 participants suffering from advanced or end stage diseases, were included. The median study duration of the cancer research was 8 weeks (16 days-11 weeks), of the HIV research 6 weeks (3-12 weeks) and of the study concentrating on Alzheimer's 2 × 6 weeks. The outcome results for cannabis/cannabinoids vs. placebo in patients with cancer were not significant for the 30% decrease in pain (RD: 0.07; 95% confidence interval (CI): -0.01 to 0.16; p = 0.07), caloric intake (SMD: 0.2; 95% CI: -0.66 to 1.06; p = 0.65) or sleep problems (SMD: -0.09; 95% CI: -0.62 to 0.43; p = 0.72).

In the treatment of HIV cannabinoids were superior to placebo for the outcome of weight change (SMD: 0.57; 95% CI: 0.22-0.92; p = 0.001). Change in appetite was significant for the treatment of HIV (SMD: 0.57; 95% CI: 0.11-1.03; p = 0.02), but not for treatment of cancer (SMD: 0.81; 95% CI: -1.14 to 2.75; p = 0.42).

Nausea/vomiting (SMD: 0.20; 95% CI: -0.03 to 0.44; p = 0.09) and health-related quality of life (HRQoL; SMD: 0.00; 95% CI: -0.19 to 0.18; p = 0.98) did not show significant differences in the therapy of the two diseases.

For the outcomes of tolerability the results were not significant for occurrence of dizziness (RD: 0.03; 95 % CI: - 0.02 to 0.08; $p=0.23$) or psychiatric diseases, such as hallucinations or psychosis (RD: - 0.01; 95 % CI: - 0.04 to 0.03; $p=0.69$) in the therapy of cancer.

The outcome of psychiatric diseases in the treatment of HIV was significant (RD: 0.05; 95 % CI: 0.00-0.11; $p=0.05$). The number of withdrawals due to adverse events, as a marker for tolerability, and the reports of serious adverse events as a measure of safety was not significantly different (RD: 1.20; 95 % CI: 0.85-1.71; $p=0.30$ and RD: 1.15; 95 % CI: 0.88-1.49; $p=0.30$, respectively).

Dronabinol vs. megestrol acetate showed a superiority of megestrol in the therapy of cancer-associated anorexia for the endpoints change of appetite (49 vs. 75 %; $p=0.0001$), weight gain (3 vs. 11 %; $p=0.02$), HRQoL ($p=0.003$) and tolerability ($p=0.03$). There was no difference in the safety of the therapies ($p=0.12$). In the treatment of HIV-associated wasting syndrome megestrol acetate was better than dronabinol for the endpoint of weight gain ($p=0.0001$), whereas tolerability and safety did not differ. In the therapy of Alzheimer's dronabinol was better than placebo in the endpoint of weight gain according to one study ($n=15$). A difference between herbal cannabis and synthetic cannabinoids, analysed by one study ($n=62$) could not be found.

Cannabinoids can lead to an increase in appetite in patients with HIV wasting syndrome but the therapy with megestrol acetate is superior to treatment with cannabinoids. The included studies were not of sufficient duration to answer questions concerning the long-term efficacy, tolerability and safety of therapy with cannabis or cannabinoids. Due to the sparse amount of data it is not possible to recommend a favoured use of cannabis or cannabinoids at this point.

Hearing Research • February 2016

Cannabinoids, cannabinoid receptors and tinnitus

Smith PF1, Zheng Y2.

1,2. Dept. of Pharmacology and Toxicology, School of Medical Sciences, University of Otago Medical School, Dunedin, New Zealand
Electronic address: paul.smith@stonebow.otago.ac.nz

<http://www.ncbi.nlm.nih.gov/pubmed/26433054>

One hypothesis suggests that tinnitus is a form of sensory epilepsy, arising partly from neuronal hyperactivity in auditory regions of the brain such as the cochlear nucleus and inferior colliculus. Although there is currently no effective drug treatment for tinnitus, anti-epileptic drugs are used in some cases as a potential treatment option. There is increasing evidence to suggest that cannabinoid drugs, i.e. cannabinoid receptor agonists, can also have anti-epileptic effects, at least in some cases and in some parts of the brain. It has been reported that cannabinoid CB1 receptors and the endogenous cannabinoid, 2-arachidonylglycerol (2-AG), are expressed in the cochlear nucleus and that they are involved in the regulation of plasticity. This review explores the question of whether cannabinoid receptor agonists are likely to be pro- or anti-epileptic in the cochlear nucleus and therefore whether cannabinoids and Cannabis itself are likely to make tinnitus better or worse.

Marijuana use trajectories during college predict health outcomes nine years post-matriculation

Arria AM1, Caldeira KM2, Bugbee BA3, Vincent KB4, O'Grady KE5.

1,3,4. Center on Young Adult Health and Development, University of Maryland School of Public Health,
Department of Behavioral and Community Health, 2387 School of Public Health Building, College Park, MD 20742, USA

5. Department of Psychology, University of Maryland, 3109 Biology-Psychology Building, College Park, MD 20742, USA

Electronic address: aarria@umd.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26778758>

Several studies have linked marijuana use with a variety of health outcomes among young adults. Information about marijuana's long-term health effects is critically needed.

Data are from a ten-year study of 1253 young adults originally recruited as first-year college students and assessed annually thereafter. Six trajectories of marijuana use during college (Non-Use, Low-Stable, Early-Divide, College-Peak, Late-Increase, Chronic) were previously derived using latent variable growth mixture modeling. Nine health outcomes assessed in Year 10 (modal age 27) were regressed on a group membership variable for the six group trajectories, holding constant demographics, baseline health status, and alcohol and tobacco trajectory group membership.

Even occasional or time-limited marijuana use might have adverse effects on physical and mental health, perhaps enduring after several years of moderation or abstinence. Reducing marijuana use frequency might mitigate such effects. Individuals who escalate their marijuana use in their early twenties might be at especially high risk for adverse outcomes.

Cerebral Cortex • February 2016

Adverse Effects of Cannabis on Adolescent Brain Development: A Longitudinal Study

Camchong J1, Lim KO2, Kumra S1.

1. Department of Psychiatry, Medical School, University of Minnesota, Minneapolis, MN, USA

2. Department of Psychiatry, Medical School, University of Minnesota, Minneapolis, MN, USA Minneapolis VA Health Care System, Minneapolis, MN, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26912785>

Cannabis is widely perceived as a safe recreational drug and its use is increasing in youth. It is important to understand the implications of cannabis use during childhood and adolescence on brain development. This is the first longitudinal study that compared resting functional connectivity of frontally mediated networks between 43 healthy controls (HCs; 20 females; age $M = 16.5 \pm 2.7$) and 22 treatment-seeking adolescents with cannabis use disorder (CUD; 8 females; age $M = 17.6 \pm 2.4$). Increases in resting functional connectivity between caudal anterior cingulate cortex (ACC) and superior frontal gyrus across time were found in HC, but not in CUD. CUD showed a decrease in functional connectivity between caudal ACC and dorsolateral and orbitofrontal cortices across time. Lower functional connectivity between caudal ACC cortex and orbitofrontal cortex at baseline predicted higher amounts of cannabis use during the following 18 months. Finally, high amounts of cannabis use during the 18-month interval predicted lower intelligence quotient and slower cognitive function measured at follow-up. These data provide compelling longitudinal evidence suggesting that repeated exposure to cannabis during adolescence may have detrimental effects on brain resting functional connectivity, intelligence, and cognitive function.

Online survey characterizing vaporizer use among cannabis users

Lee DC1, Crosier BS2, Borodovsky JT2, Sargent JD3, Budney AJ2.

1,2. Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
3. C. Everett Koop Institute, Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH, USA
Electronic address: Dustin.C.Lee@Dartmouth.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/26774946>

Along with changes in cannabis laws in the United States and other countries, new products for consuming cannabis are emerging, with unclear public health implications. Vaporizing or “vaping” cannabis is gaining popularity, but little is known about its prevalence or consequences.

An online survey was distributed through Facebook ads targeting individuals with interests related to cannabis use. The sample comprised 2910 cannabis users (age: 18-90, 84% male, 74% Caucasian).

A majority (61%) endorsed lifetime prevalence of ever vaping, 37% reported vaping in the past 30 days, 20% reported vaping more than 100 lifetime days, and 12% endorsed vaping as their preferred method.

Compared to those that had never vaped, vaporizer users were younger, more likely to be male, initiated cannabis at an earlier age, and were less likely to be African American. Those that preferred vaping reported it to be healthier, better tasting, produced better effects, and more satisfying. Only 14% reported a reduction in smoking cannabis since initiating vaping, and only 5% mixed cannabis with nicotine in a vaporizer. Many cannabis users report vaping cannabis, but currently only a small subset prefers vaping to smoking and reports frequent vaping.

Increases in availability and marketing of vaping devices, and the changing legal status of cannabis in the United States and other countries may influence patterns of use. Frequent monitoring is needed to assess the impact of changing cannabis laws and regulations.

Medical use of cannabis products: Lessons to be learned from Israel and Canada

Ablin J1, Ste-Marie PA2,3, Schäfer M4, Häuser W5,6, Fitzcharles MA2,3.

1. Institute of Rheumatology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
2. Division of Rheumatology, McGill University, Montreal, Quebec, Canada.
3. Alan Edwards Pain Management Unit, McGill University Health Center, Montreal, Quebec, Canada.
4. Department of Anesthesiology and Intensive Care Medicine, Charité University, Berlin Campus Virchow Klinikum, Berlin, Germany.
5. Klinikum Saarbrücken gGmbH, Innere Medizin 1, Winterberg 1, 66119, Saarbrücken, Germany. whaeuser@klinikum-saarbruecken.de.
6. Department Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany
whaeuser@klinikum-saarbruecken.de.

<http://www.ncbi.nlm.nih.gov/pubmed/26767992>

The German government intends to reduce the barriers for the medical use of cannabis products. A discussion on the indications and contraindications of the medical use of cannabis and on the changes of the regulatory framework has already begun in Germany. It is useful to draw from the experiences of other countries with a more liberal medical use of cannabis.

The Israeli and Canadian experience is outlined by physicians who have been charged with expertise on the medical use of cannabis by their jurisdiction.

In Israel, only the plant-based cannabinoid nabiximol (mixture of tetrahydrocannabinol/cannabidiol) can be prescribed for spasticity/chronic pain in multiple sclerosis and for cancer pain. The costs of nabiximole

are reimbursed by some, but not by all health maintenance organizations. The medical use of marijuana is permitted; however, it is strictly regulated by the government. Selected companies are allowed to produce marijuana for medical use, and only certain physicians are licensed to prescribe marijuana as a therapeutic drug for specific indications such as chronic neuropathic, and cancer pain, inflammatory bowel diseases, or posttraumatic stress disorder if conventional treatments have failed. The costs of marijuana are not reimbursed by health insurance companies. In Canada, synthetic cannabinoids and the plant-based (nabiximol) are licensed for neuropathic and cancer pain, HIV-related anorexia and chemotherapy-associated nausea. The costs of these synthetic cannabinoids are covered by health insurance companies. The medical use of marijuana as a treatment option is allowed for individual patients

suffering from any medical condition when authorized by a medical practitioner or nurse. Licensed producers are the only source for patients to newly access medical cannabis, although those with previous permission to grow may continue cultivation at the present time. The costs of marijuana are not reimbursed by health insurance companies. There are multiple contraindications for the medical use of cannabis products in both countries.

The use of standardized, synthetic, and plant-based cannabis products should be allowed in Germany for defined medical conditions when high-level evidence of efficacy and safety exists. The costs should be reimbursed by the health insurance companies. Contraindications for the medical use of cannabis should be defined. Growing marijuana by patients for their medical use should not be allowed.

Ligands for cannabinoid receptors, promising anticancer agents

Nikan M1, Nabavi SM2, Manayi A3.

1. Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
2. Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
3. Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
Electronic address: Manayi@sina.tums.ac.ir

<http://www.ncbi.nlm.nih.gov/pubmed/26764235>

Cannabinoid compounds are unique to cannabis and provide some interesting biological properties. These compounds along with endocannabinoids, a group of neuromodulator compounds in the body especially in brain, express their effects by activation of G-protein-coupled cannabinoid receptors, CB1 and CB2. There are several physiological properties attributed to the endocannabinoids including pain relief, enhancement of appetite, blood pressure lowering during shock, embryonic development, and blocking of working memory. On the other hand, activation of endocannabinoid system may be suppresses evolution and progression of several types of cancer. According to the results of recent studies, CB receptors are over-expressed in cancer cell lines and application of multiple cannabinoid or cannabis-derived compounds reduce tumor size through decrease of cell proliferation or induction of cell cycle arrest and apoptosis along with desirable effect on decrease of tumor-evoked pain. Therefore, modulation of endocannabinoid system by inhibition of fatty acid amide hydrolase (FAAH), the enzyme, which metabolized endocannabinoids, or application of multiple cannabinoid or cannabis-derived compounds, may be appropriate for the treatment of several cancer subtypes. This review focuses on how cannabinoid affect different types of cancers.

Harefuah • February 2016

MEDICAL CANNABIS

By T. Naftali

<http://www.ncbi.nlm.nih.gov/pubmed/27215115>

The cannabis plant has been known to humanity for centuries as a remedy for pain, diarrhea and inflammation. Current research is inspecting the use of cannabis for many diseases, including multiple sclerosis, epilepsy, dystonia, and chronic pain. In inflammatory conditions cannabinoids improve pain in rheumatoid arthritis and pain and diarrhea in Crohn's disease. Despite their therapeutic potential, cannabinoids are not free of side effects including psychosis, anxiety, paranoia, dependence and abuse. Controlled clinical studies investigating the therapeutic potential of cannabis are few and small, whereas pressure for expanding cannabis use is increasing. Currently, as long as cannabis is classified as an illicit drug and until further controlled studies are performed, the use of medical cannabis should be limited to patients who failed conventional better established treatment.

ACS Medicinal Chemistry Letters • February 2016

Discovery of KLS-13019, a Cannabidiol-Derived Neuroprotective Agent, with Improved Potency, Safety, and Permeability

Kinney WA1, McDonnell ME1, Zhong HM2, Liu C2, Yang L2, Ling W2, Qian T2, Chen Y2, Cai Z2, Petkanas D1, Brenneman DE1.

1. KannaLife Sciences, 3805 Old Easton Road, Doylestown, Pennsylvania 18902, USA
2. PharmaAdvance, Inc., 6 Dongsheng West Road, Building D1, Jiangyin, Jiangsu Province, P. R. China

<http://www.ncbi.nlm.nih.gov/pubmed/27096053>

Cannabidiol is the nonpsychoactive natural component of *C. sativa* that has been shown to be neuroprotective in multiple animal models. Our interest is to advance a therapeutic candidate for the orphan indication hepatic encephalopathy (HE). HE is a serious neurological disorder that occurs in patients with cirrhosis or liver failure. Although cannabidiol is effective in models of HE, it has limitations in terms of safety and oral bioavailability. Herein, we describe a series of side chain modified resorcinols that were designed for greater hydrophilicity and “drug likeness”, while varying hydrogen bond donors, acceptors, architecture, basicity, neutrality, acidity, and polar surface area within the pendent group. Our primary screen evaluated the ability of the test agents to prevent damage to hippocampal neurons induced by ammonium acetate and ethanol at clinically relevant concentrations. Notably, KLS-13019 was 50-fold more potent and >400-fold safer than cannabidiol and exhibited an in vitro profile consistent with improved oral bioavailability.

Limitations to the Dutch cannabis toleration policy: Assumptions underlying the reclassification of cannabis above 15% THC

Van Laar M1, Van Der Pol P2, Niesink R3.

1,2. Trimbos Institute, Da Costakade 45, 3521 VS Utrecht, The Netherlands

3. Trimbos Institute, Da Costakade 45, 3521 VS Utrecht, The Netherlands

Open University of The Netherlands, PO-Box 2960, 6401 DL Heerlen, The Netherlands

Electronic address: mlaar@trimbos.nl

<http://www.ncbi.nlm.nih.gov/pubmed/27471078>

The Netherlands has seen an increase in $\Delta 9$ -tetrahydrocannabinol (THC) concentrations from approximately 8% in the 1990s up to 20% in 2004. Increased cannabis potency may lead to higher THC-exposure and cannabis related harm. The Dutch government officially condones the sale of cannabis from so called 'coffee shops', and the Opium Act distinguishes cannabis as a Schedule II drug with 'acceptable risk' from other drugs with 'unacceptable risk' (Schedule I). Even in 1976, however, cannabis potency was taken into account by distinguishing hemp oil as a Schedule I drug. In 2011, an advisory committee recommended tightening up legislation, leading to a 2013 bill proposing the reclassification of high potency cannabis products with a THC content of 15% or more as a Schedule I drug. The purpose of this measure was twofold: to reduce public health risks and to reduce illegal cultivation and export of cannabis by increasing punishment. This paper focuses on the public health aspects and describes the (explicit and implicit) assumptions underlying this '15% THC measure', as well as to what extent these are supported by scientific research. Based on scientific literature and other sources of information, we conclude that the 15% measure can provide in theory a slight health benefit for specific groups of cannabis users (i.e., frequent users preferring strong cannabis, purchasing from coffee shops, using 'steady quantities' and not changing their smoking behaviour), but certainly not for all cannabis users. These gains should be weighed against the investment in enforcement and the risk of unintended (adverse) effects. Given the many assumptions and uncertainty about the nature and extent of the expected buying and smoking behaviour changes, the measure is a political choice and based on thin evidence.

Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study

Mokrysz C1, Landy R2, Gage SH3, Munafò MR3, Roiser JP4, Curran HV5.

1. Clinical Psychopharmacology Unit, University College London, London, UK
2. Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK
3. MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK
4. Institute of Cognitive Neuroscience, University College London, London, UK
5. Clinical Psychopharmacology Unit, University College London, London, UK
c.mokrysz.12@ucl.ac.uk

Full text with 55 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4724860/>

There is much debate about the impact of adolescent cannabis use on intellectual and educational outcomes. We investigated associations between adolescent cannabis use and IQ and educational attainment in a sample of 2235 teenagers from the Avon Longitudinal Study of Parents and Children. By the age of 15, 24% reported having tried cannabis at least once. A series of nested linear regressions was employed, adjusted hierarchically by pre-exposure ability and potential confounds (e.g. cigarette and alcohol use, childhood mental-health symptoms and behavioural problems), to test the relationships between cumulative cannabis use and IQ at the age of 15 and educational performance at the age of 16. After full adjustment, those who had used cannabis 50 times did not differ from never-users on either IQ or educational performance. Adjusting for group differences in cigarette smoking dramatically attenuated the associations between cannabis use and both outcomes, and further analyses demonstrated robust associations between cigarette use and educational outcomes, even with cannabis users excluded. These findings suggest that adolescent cannabis use is not associated with IQ or educational performance once adjustment is made for potential confounds, in particular adolescent cigarette use. Modest cannabis use in teenagers may have less cognitive impact than epidemiological surveys of older cohorts have previously suggested.

Neural Plasticity • January 2016

The Endocannabinoid System as a Therapeutic Target in Glaucoma

Cairns EA1, Baldrige WH2, Kelly ME3.

1. Department of Pharmacology, Dalhousie University, Halifax, NS, Canada

2. Department of Medical Neuroscience, Dalhousie University, Halifax, NS, Canada
Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada

3. Department of Pharmacology, Dalhousie University, Halifax, NS, Canada
Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada

Full text with 94 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737462/>

Glaucoma is an irreversible blinding eye disease which produces progressive retinal ganglion cell (RGC) loss. Intraocular pressure (IOP) is currently the only modifiable risk factor, and lowering IOP results in reduced risk of progression of the disorder. The endocannabinoid system (ECS) has attracted considerable attention as a potential target for the treatment of glaucoma, largely due to the observed IOP lowering effects seen after administration of exogenous cannabinoids. However, recent evidence has suggested that modulation of the ECS may also be neuroprotective. This paper will review the use of cannabinoids in glaucoma, presenting pertinent information regarding the pathophysiology of glaucoma and how alterations in cannabinoid signalling may contribute to glaucoma pathology. Additionally, the mechanisms and potential for the use of cannabinoids and other novel agents that target the endocannabinoid system in the treatment of glaucoma will be discussed.

Cannabinoids in the Treatment of Epilepsy

Friedman D, Devinsky O.

To the Editor:

The need for effective antiseizure drugs in addition to available compounds is obvious. The review article by Friedman and Devinsky (Sept. 10 issue)¹ highlights experimental data that suggest antiseizure effects of cannabinoids. However, the overview of studies indicating that cannabinoids can also provoke seizures seems incomplete, since studies examining the effects of recreational use of cannabis and other studies suggest serious adverse effects, including clinically significant drug–drug interactions, in patients who have epilepsy with or without underlying conditions.²⁻⁵ I agree that data are lacking from well-controlled clinical trials on the antiseizure properties of cannabinoids. However, it is well documented that cannabinoids can also provoke seizures, depending on the content of the cannabidiol and $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC), the ratio of these two agents in the products used, and the underlying conditions in the patient. Thus, the authors' suggestion regarding relaxation of the regulatory status of cannabis-derived drugs seems less applicable to the treatment of epilepsy than to the treatment of other conditions in which the therapeutic application of cannabinoids has been considered. Trials should be performed cautiously, with carefully planned safety monitoring and early interim analyses by independent boards, in order to not overlook subgroups of patients who may have an undesirable increase in epileptic activity.

Joep Killestein, M.D., Ph.D., VU University Medical Center, Amsterdam, the Netherlands
No potential conflict of interest relevant to this letter was reported
j.killestein@vumc.nl

The authors reply:

We agree with the assessment by Killestein. Studies showing that $\Delta 9$ -THC or synthetic cannabinoid agonists can provoke or exacerbate seizures or interact with other drugs suggest that caution should be used when studying and administering medications containing these compounds. In our article, we noted anecdotal reports of seizures that were provoked by cannabis use,¹ and we noted that cannabidiol can increase the levels of the N-desmethyl metabolite of clobazam and increase the antiseizure and toxic effects of this drug.² However, although some currently marketed antiseizure medications are associated with clinically significant drug–drug interactions or may rarely provoke seizures in some patients, these side effects do not outweigh the overall benefit of the drugs. At this time, we think that the weight of the limited evidence suggests that there may be a benefit associated with some cannabinoids in the treatment of epilepsy and little solid scientific evidence that cannabis that contains various mixtures of cannabidiol and $\Delta 9$ -THC can provoke seizures. Therefore, we support the relaxation of restrictions to allow further scientific study. We do not yet know the overall risks and benefits of cannabinoids in the treatment of epilepsy, but we hope that randomized, controlled studies will answer these questions soon.

Daniel Friedman, M.D. and Orrin Devinsky, M.D., New York University Langone School of Medicine, New York, NY
daniel.friedman@nyumc.org

In addition to previously disclosed financial relationships, Dr. Friedman reports the following financial relationships in existence at the time of publication of the review article: receiving consulting fees through his institution from Acorda Therapeutics and Alexza Pharmaceuticals and grant support through his institution from UCB. Dr. Friedman's disclosure form has been updated at NEJM.org. Since publication of their article, Dr. Friedman reports receiving consulting fees from Cyberonics, and Dr. Devinsky reports serving on the scientific advisory board for and owning stock in Pairnomix. No further potential conflict of interest relevant to this letter was reported. This article was published on December 16, 2015, at NEJM.org.

Full text with 7 references

<http://www.nejm.org/doi/full/10.1056/NEJMra1407304>

Therapies In Advanced Neurological Disorders • January 2016

Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis

Zettl UK1, Rommer P2, Hipp P3, Patejdl R4.

1. Department of Neurology, University of Rostock, Gehlsheimer Straße 20, D-18147 Rostock, Germany

2. Department of Neurology, University of Rostock, Germany

3. Saproma, Roetgen, Germany

4. Department of Neurology, University of Rostock, Germany Oscar-Langendorff-Institute of Physiology, University of Rostock, Germany

Full text with 102 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4710104/>

Spasticity, one of the main symptoms of multiple sclerosis (MS), can affect more than 80% of MS patients during the course of their disease and is often not treated adequately. δ -9-Tetrahydrocannabinol-cannabidiol (THC-CBD) oromucosal spray is a plant-derived, standardized cannabinoid-based oromucosal spray medicine for add-on treatment of moderate to severe, resistant multiple sclerosis-induced spasticity. This article reviews the current evidence for the efficacy and safety, with dizziness and fatigue as the most common treatment-related adverse events, being mostly mild to moderate in severity. Results from both randomized controlled phase III studies involving about 1,600 MS patients or 1,500 patient-years and recently published studies on everyday clinical practice involving more than 1,000 patients or more than 1,000 patient-years are presented.

Microglial Cells as a Link between Cannabinoids and the Immune Hypothesis of Psychiatric Disorders

Lisboa SF1, Gomes FV2, Guimaraes FS1, Campos AC1.

1. Department of Pharmacology, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil
Center of Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Ribeirão Preto, Brazil
2. Department of Neuroscience, University of Pittsburgh , Pittsburgh, PA , USA

Full text with 144 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729885/>

Psychiatric disorders are one of the leading causes of disability worldwide. Although several therapeutic options are available, the exact mechanisms responsible for the genesis of these disorders remain to be fully elucidated. In the last decade, a body of evidence has supported the involvement of the immune system in the pathophysiology of these conditions. Microglial cells play a significant role in maintaining brain homeostasis and surveillance. Dysregulation of microglial functions has been associated with several psychiatric conditions. Cannabinoids regulate the brain-immune axis and inhibit microglial cell activation. Here, we summarized evidence supporting the hypothesis that microglial cells could be a target for cannabinoid influence on psychiatric disorders, such as anxiety, depression, schizophrenia, and stress-related disorders.

Paediatric Child Health • January 2016

Is the medical use of cannabis a therapeutic option for children?

Rieder MJ; Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee.

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758425/>

Cannabis is a psychoactive compound with a long history of recreational and therapeutic use. Current considerations regarding cannabis use for medical purposes in children have been stimulated by recent case reports describing its beneficial effect with refractory epilepsy. Overall, there are insufficient data to support either the efficacy or safety of cannabis use for any indications in children, and an increasing body of data suggests possible harm, most importantly in specific conditions. The potential for cannabis as a therapeutic agent must be evaluated carefully for both efficacy and safety in treating specific paediatric health conditions. Smoking is not an acceptable mode of drug delivery for children. The use of cannabis for medical purposes in specific cases should not be construed as a justification for recreational cannabis use by adolescents. Recommendations for therapeutic use in exceptional paediatric cases are offered, always providing that this treatment course is carefully evaluated in individuals and in ongoing, well-designed research studies to determine safety and efficacy.

Exploring Butane Hash Oil Use: A Research Note

Miller BL1, Stogner JM2, Miller JM3.

1. Associate Professor, Department of Criminal Justice and Criminology, Georgia Southern University, Statesboro, GA, USA
2. Assistant Professor, Department of Criminal Justice and Criminology, University of North Carolina at Charlotte, Charlotte, NC, USA
3. Professor, Department of Criminology and Criminal Justice, University of North Florida, Jacksonville, FL, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26800050>

The practice of “dabbing” has seen an apparent upswing in popularity in recent months within American drug subcultures.

“Dabbing” refers to the use of butane-extracted marijuana products that offer users much higher tetrahydrocannabinol content than flower cannabis through a single dosage process. Though considerably more potent than most marijuana strains in their traditional form, these butane hash oil products and the practice of dabbing are underexplored in the empirical literature, especially in prohibition states. A mixed-methods evaluation of a federally funded treatment program for drug-involved offenders identified a small sample ($n = 6$) of butane hash oil users and generated focus group interview data on the nature of butane hash oil, the practice of dabbing, and its effects.

Findings inform discussion of additional research needed on butane hash oil and its implications for the ongoing marijuana legalization debate, including the diversity of users, routes of administration, and differences between retail/medical and prohibition states.

A case of butane hash oil (marijuana wax)-induced psychosis

Keller CJ^{1,2}, Chen EC^{1,2}, Brodsky K^{1,2}, Yoon JH^{1,2}.

1. Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, USA

2. VA Palo Alto Health Care System, Palo Alto, California, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26820171>

Marijuana is one of the most widely used controlled substances in the United States. Despite extensive research on smoked marijuana, little is known regarding the potential psychotropic effects of marijuana “wax,” a high-potency form of marijuana that is gaining in popularity.

The authors present a case of “Mr. B,” a 34-year-old veteran who presented with profound psychosis in the setting of recent initiation of heavy, daily marijuana wax use. He exhibited incoherent speech and odd behaviors and appeared to be in a dream-like state with perseverating thoughts about his combat experience. His condition persisted despite treatment with risperidone 4 mg twice a day (BID), but improved dramatically on day 8 of hospitalization with the return of baseline mental function. Following discharge, Mr. B discontinued all marijuana use and did not exhibit the return of any psychotic symptoms.

This study highlights the need for future research regarding the potential medical and psychiatric effects of new, high-potency forms of marijuana. Could cannabis have a dose-dependent impact on psychosis? What other potential psychiatric effects could emerge heretofore unseen in lower potency formulations? Given the recent legalization of marijuana, these questions merit timely exploration.

Progress In Neuropsychopharmacology And Biological Psychiatry • January 2016

Therapeutic potential of cannabis-related drugs

By S. P. Alexander

Life Sciences, University of Nottingham Medical School, Nottingham NG7 2UH, England, UK
Electronic address: Steve.alexander@nottingham.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/26216862>

In this review, I will consider the dual nature of Cannabis and cannabinoids. The duality arises from the potential and actuality of cannabinoids in the laboratory and clinic and the 'abuse' of Cannabis outside the clinic. The therapeutic areas currently best associated with exploitation of Cannabis-related medicines include pain, epilepsy, feeding disorders, multiple sclerosis and glaucoma. As with every other medicinal drug of course, the 'trick' will be to maximise the benefit and minimise the cost. After millennia of proximity and exploitation of the Cannabis plant, we are still playing catch up with an understanding of its potential influence for medicinal benefit.

Cannabinoid-induced autophagy: Protective or death role?

Costa L1, Amaral C2, Teixeira N2, Correia-da-Silva G2, Fonseca BM3.

1. Departamento de Biologia, Universidade de Aveiro, Portugal

UCIBIO, REQUIMTE, Laboratório de Bioquímica, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Portugal

2,3. UCIBIO, REQUIMTE, Laboratório de Bioquímica, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Portugal

Electronic address: brunofonseca@ff.up.pt

<http://www.ncbi.nlm.nih.gov/pubmed/26732541>

Autophagy, the “self-digestion” mechanism of the cells, is an evolutionary conserved catabolic process that targets portions of cytoplasm, damaged organelles and proteins for lysosomal degradation, which plays a crucial role in development and disease. Cannabinoids are active compounds of *Cannabis sativa* and the most prevalent psychoactive substance is $\Delta(9)$ -tetrahydrocannabinol (THC). Cannabinoid compounds can be divided in three types: the plant-derived natural products (phytocannabinoids), the cannabinoids produced endogenously (endocannabinoids) and the synthesized compounds (synthetic cannabinoids). Various studies reported a cannabinoid-induced autophagy mechanism in cancer and non-cancer cells. In this review we focus on the recent advances in the cannabinoid-induced autophagy and highlight the molecular mechanisms involved in these processes.

Expert Reviews In Neurotherapy • January 2016

Cannabidiol as potential treatment in refractory pediatric epilepsy

Paolino MC1, Ferretti A1, Papetti L2, Villa MP1, Parisi P1.

1. Child Neurology, Headache Paediatric Center, Paediatric Sleep Disorders, NESMOS Department, Chair of Pediatrics, Faculty of Medicine and Psychology, Sapienza University, c/o Sant'Andrea Hospital, Rome, Italy
2. Department of Pediatrics, Child Neurology Division, Sapienza University of Rome, Rome, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/26567560>

In recent years there has been great scientific and public interest focused on the therapeutic potential of compounds derived from cannabis for the treatment of refractory epilepsy in children. From in vitro and in vivo studies on animal models, cannabidiol (CBD) appears to be a promising anticonvulsant drug with a favorable side-effect profile. In humans, CBD efficacy and safety is not supported by well-designed trials and its use has been described by anecdotal reports. It will be necessary to investigate CBD safety, pharmacokinetics and interaction with other anti-epileptic drugs (AEDs) alongside performing double-blinded placebo-controlled trials in order to obtain conclusive data on its efficacy and safety in children.

Journal Of Psychoactive Drugs • January 2016

Stigma Among California's Medical Marijuana Patients

Travis D. Satterlund, Ph.D., J.D.,¹ Juliet P. Lee, Ph.D.,² and Roland S. Moore, Ph.D.²

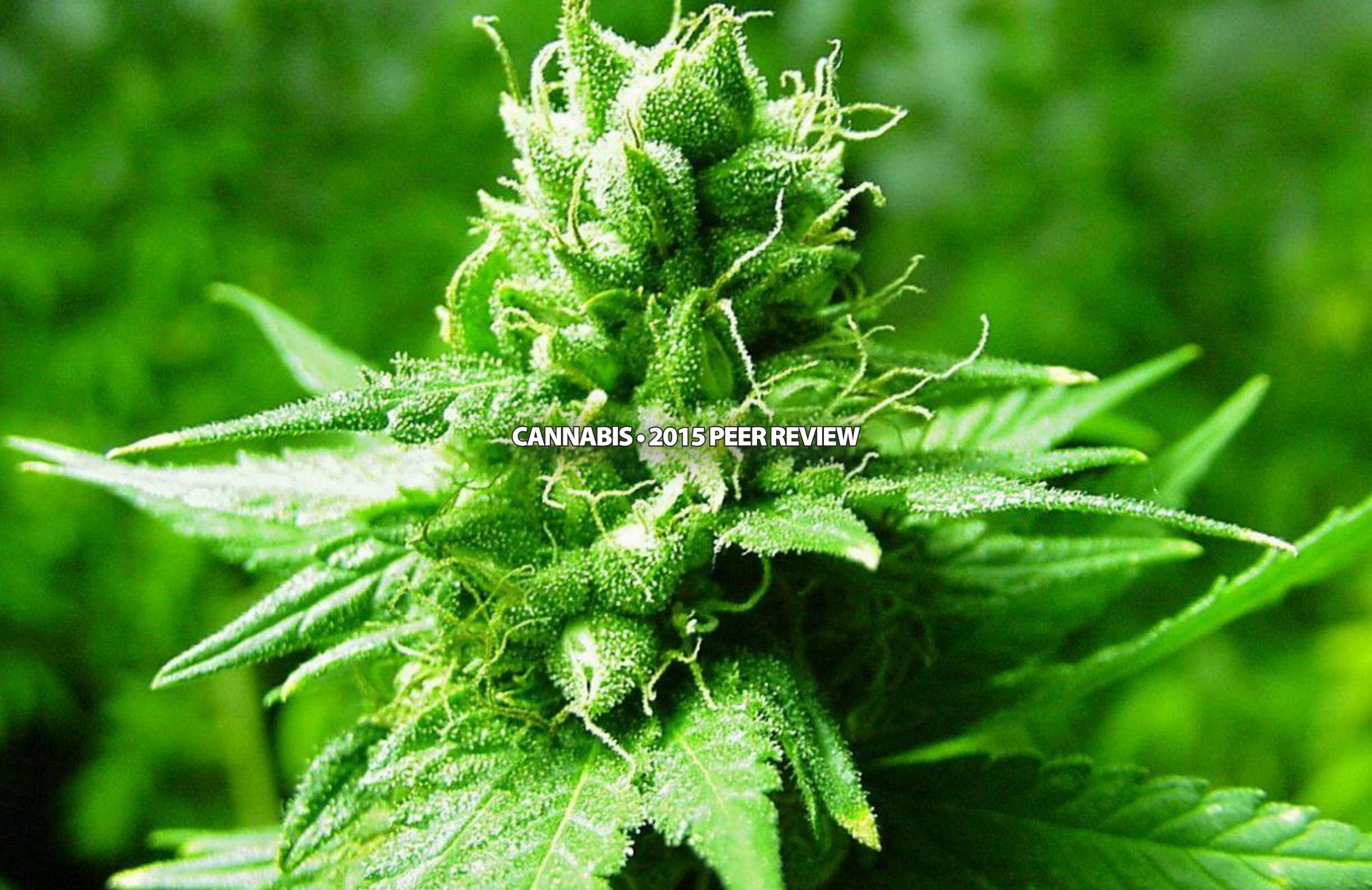
1. Research Analyst, Center for Program Design and Evaluation, Dartmouth College, Lebanon, NH.

2. Senior Research Scientist, the Prevention Research Center of the Pacific Institute for Research and Evaluation, Oakland

Full text with 48 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341951/>

The enactment of California's Proposition 215 stipulates that patients may use marijuana for medical reasons, provided that it is recommended by a physician. Yet, medical marijuana patients risk being stigmatized for this practice. This paper examines the way in which medical marijuana patients perceive and process stigma, and how it affects their interactions and experiences with others. Eighteen semi-structured interviews of medical marijuana patients were carried out using a semi-structured interview guide. Most patients circumvented their own physicians in obtaining a recommendation to use medicinal marijuana, and also used a host of strategies in order to justify their medical marijuana use to family, friends and colleagues in order to stave off potential stigma. The stigmatization of medical marijuana thus has a profound effect on how patients seek treatment, and whether they seek medical marijuana treatment at all.



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It's Not Your Mother's Marijuana: Effects on Maternal-Fetal Health and the Developing Child

Tamara D. Warner, PhD,¹ Dikea Roussos-Ross, MD,² and Marylou Behnke, MD¹

1. University of Florida, Department of Pediatrics, P.O. Box 100296, Gainesville, FL

2. University of Florida, Department of Obstetrics and Gynecology, P.O. Box 100294, Gainesville, FL

Tamara D. Warner: warner@peds.ufl.edu

Full text with 99 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254522/>

Pro-marijuana advocacy efforts exemplified by the “medical” marijuana movement, coupled with the absence of conspicuous public health messages about the potential dangers of marijuana use during pregnancy, could lead to greater use of today’s more potent marijuana, which could have significant short- and long-term consequences. This article will review the current literature regarding the effects of prenatal marijuana use on the pregnant woman and her offspring.

Effects of Prenatal Marijuana Use

A list of the possible pregnancy-related effects of prenatal marijuana use can be found in Box 3. Marijuana easily passes through the maternal circulation, into the placenta, and then fetus. It is also found in breast milk. Marijuana can be detected in umbilical cord blood, neonatal urine, and meconium.

Pre-clinical studies are important as they can: (1) provide a level of control for confounding variables not achievable in clinical studies, (2) offer a framework for developing hypotheses for further study in human populations, and (3) help to identify the pathologic changes that underlie the medical and behavioral changes observed in

Box 3

Possible Pregnancy-Related Effects of Prenatal Marijuana Use

- Decreased male fertility
- Decreased ovulation
- Altered hormones (prolactin, FSH, LH, estrogen)
- Altered oviductal transport, embryo implantation, maintenance of pregnancy
- Altered placental blood flow
- Intrauterine growth restriction
- Decreased gestational age
- Decreased birth weight

clinical studies. A full discussion of the pre-clinical literature is beyond the scope of this review and the reader is referred to pertinent studies and reviews available in the extant literature.^{27–30} Research into the effects of THC in humans began in the late 1800s with two major advances occurring when the main psychoactive compound in marijuana, THC, was identified by Gaoni and Mechoulam in 1964³¹ and when the existence of cannabinoid receptors, called the endocannabinoid system, was confirmed by DeVane et al in 1988.³²

Cannabinoid receptors are found in various tissues throughout the human body, including the brain and uterine decidua. Thus the physiologic

functions of the endocannabinoid system are important to both early embryonic development and synaptic brain plasticity. However, exposure to exogenous cannabinoids could result in pathophysiologic changes secondary to the longer binding of THC to the receptors as compared to naturally occurring endocannabinoids. With regard to early embryonic development, it is possible that exogenous cannabinoids could significantly disrupt regulation of blastocyst maturation, oviductal transport, implantation, and pregnancy maintenance. In addition, THC acts as an *in vivo* weak

competitor of the estrogen receptor, producing a primary estrogen effect in male and female rats,³³ stifles trophoblast cell proliferation, and inhibits successful placenta-tion, possibly producing other pregnancy related complications.^{34,35}

In the brain, cannabinoids alter executive functions in the pre-frontal cortex, including working memory, attention, and cognitive flexibility. Additionally, the release of neurotransmitters such as dopamine, serotonin, and acetylcholine, each of which affects cognitive functions in the prefrontal cortex, as well as behavior and mood, has been shown to be altered in the face of cannabinoid exposure.

Marijuana and Infertility

Human studies on male subjects have shown disruptions in the hypothalamic-pituitary-testicular axis with decreased luteinizing hormone, decreased testosterone, oligospermia and decreased sperm motility, thus possibly affecting male infertility.³⁶ Likewise, in women, chronic marijuana exposure has been associated with suppressed ovulation, altered prolactin, follicle-stimulating hormone, and luteinizing hormone, and estrogen.^{37,38}

Pregnancy-Related Complications

The endocannabinoid system is present in the uterine decidua, thus suggesting possible involvement in pregnancy complications such as miscarriage, pre-eclampsia, growth restriction and preterm labor.³⁵ Additionally, first trimester placentas express cannabinoid receptors, further implicating the role that alterations in the endocannabinoid system may play in pregnancy complications. Marijuana use during pregnancy has been shown to be associated with an increased fetal pulsatility index and resistance index of the uterine artery,³⁹ suggestive of increased placental resistance.⁴⁰ These findings may provide a partial explanation for intrauterine growth restriction.⁴¹

Fetal Growth and Birth Outcomes

Available data to this point do not reveal marijuana-associated fetal teratogenicity. Studies on the effects of prenatal maternal marijuana use on fetal growth and birth outcomes have yielded inconsistent results. A 2013 review of studies on prena-

tal marijuana exposure by Huizink⁴¹ specifically examined fetal growth, birth outcomes and early infant development using data from several sources including three prospective longitudinal studies: (1) the Ottawa Prenatal Prospective Study (OPPS), which began in 1978 and enrolled a predominantly middle-class, low-risk, Caucasian sample from Ottawa, Canada⁴²; (2) the Maternal Health Practice and Child Development Study (MHPCD), which started in 1982 and enrolled a high-risk, low socioeconomic status mixed Caucasian and African-American sample from Pittsburgh, PA⁴³ and (3) the Generation R study, which started in 2010 and recruited a multi-ethnic population-based cohort in Rotterdam, the Netherlands.⁴⁴ Of the three cohorts, only the Generation R study has examined fetal growth through ultrasound assessments several times during pregnancy.

Fetal Growth

A study using elective mid-gestation aborted fetuses (17 to 22 weeks) who were exposed to marijuana, tobacco, and alcohol demonstrated decreased weight and decreased foot length that was associated with marijuana exposure after controlling for other drug exposures.⁴⁵ No association was found between prenatal marijuana exposure and body length or head circumference after controlling for covariates.⁴⁵ Results from the Generation R study have shown: reduced fetal growth from the 2nd trimester onwards, particularly for mothers who used early marijuana during pregnancy or throughout the entire pregnancy.⁴⁶

Birth Outcomes

Results have differed between the three longitudinal cohorts described above with the OPPS reporting reduced gestational age but no differences in birth weight,⁴⁷ the MPHCD reporting reduced birth length after 1st trimester exposure and unexpectedly, increased birth weight after 3rd trimester exposure,⁴⁸ and Generation R reporting reduced birth weight.⁴⁶

Studies drawn from other sources yield conflicting results. A recent study by Hayatbakhsh et al. reported lower birth weight, by an average of 375 grams, lower gestational age, shorter body length and an increase in NICU admissions due to marijuana exposure after adjusting for tobacco, alcohol and other illicit drug exposures.⁴⁹ However, studies reporting no association between marijuana use and fetal growth in-

clude the Maternal Lifestyle Study,⁵⁰ a multicenter, prospective study of 8,600 women (which also included cocaine use)⁵¹ and the Avon Longitudinal Study of Pregnancy cohort of more than 12,000 pregnant women.⁵² A population-based study using data from the National Birth Defects Prevention Study also found no associations between marijuana use during pregnancy and mean birth weight, gestational age, low birth weight or preterm delivery.⁵³

Maternal Marijuana Use and Lactation

There is a paucity of data regarding the effects of maternal marijuana use on breastfeeding and infant outcomes. Small to moderate amounts of THC are secreted into breastmilk after maternal use with significant absorption by the infant. However, identification of side effects in the lactation-exposed infant are inconsistent,^{54,55} and no long-term outcome studies are available. As noted in the previous section, studies of the endocannabinoid system from both the animal and human literature indicate there are neurobehavioral complications after marijuana exposure during pregnancy, raising the possibility of complications after exposure during lactation, as well. More detailed information is available in recent reviews by Rowe et al.⁵⁶ and Hill and Reed.²⁵ At the present time, the American Academy of Pediatrics recommends that women who are using street drugs, including marijuana, not breastfeed their infants.⁵⁷

Developmental Outcomes Of Prenatal Marijuana Exposure: Neonatal Period To Early Adulthood

As outlined previously, several prospective, longitudinal cohort studies have evaluated the effects of prenatal marijuana exposure on offspring. However, the OPPS and the MHPCD are the only cohorts that have been followed into adolescence and early adulthood. Despite the demographic differences between these two cohorts, when the results overlap, they are remarkably consistent.

Neonatal Withdrawal and Neurobehavior

Neonatal withdrawal from marijuana exposure has not been reported in any of the prospective, longitudinal studies. Evidence of altered state regulation, manifested

as increased startles and tremors, was identified in the OPPS sample during the first week of life⁵⁸ using the Neonatal Behavioral Assessment Scale (NBAS)⁵⁹ with similar results found again at 9 and 30 days⁶⁰ using the Prechtl⁶¹ neurologic examination. Poorer visual habituation and responses were also noted during the first week of life,⁵⁸ but these problems were not seen again at 9 and 30 days.⁶⁰ No effects were reported from the MHPCD on newborn behavior using the NBAS.⁴³ However, exposed newborns demonstrated altered sleep patterns with a decrease in quiet sleep and increased sleep motility suggesting increased activity in the noradrenergic system.⁶² Other newborn studies have demonstrated abnormal newborn cry,⁶³ also suggestive of increased arousal. Other investigators have found no abnormalities in infant behavior.^{64,65}

Prenatal Marijuana Exposure and Outcomes from Late Infancy to Young Adulthood

This section focuses on the areas of development where prenatal marijuana exposure appears to have a significant impact: executive function, attention, achievement, and behavior. Findings in other areas of development can be summarized as follows with details found in table 3.

Executive Function/Attention

Of importance, both cohorts have reported a negative effect of prenatal marijuana exposure on specific areas of cognition related to executive function at age 3 years,⁷¹ 4 years,⁶⁷ and 6 years.⁸¹ Findings in both cohorts include poorer scores on memory and verbal measures. At 6 years, Fried et al.⁸² reported a negative effect of prenatal marijuana exposure on the attentiveness of subjects using a vigilance task. This finding is consistent with that from the MHPCD at 6 years which showed increased impulsivity on a vigilance task.⁸³ Children ages 9 to 12 in both the OPPS and the MHPCD showed poorer abstract/visual reasoning, impulse control, hypothesis testing, and visual problem solving.^{84–86} At age 10, marijuana-exposed youth in the MHPCD were more likely to exhibit hyperactivity, impulsivity, and inattention, according to maternal report.⁸⁷ Finally, two studies from the OPPS when subjects were 13 to 16 years old documented continued problems with executive function and attention. Adolescents with prenatal marijuana exposure demonstrated decreased attentional

stability as evidenced by a decreasing consistency in reaction time as the test progressed and by an increase in errors of omission.⁸⁸ The exposed adolescents also had poorer scores on two measures indicative of problems with visual memory, analysis, and integration.⁶⁹ Several additional studies from the Ottawa sample have used fMRI to evaluate the subjects between 18 to 22 years. While performing a response inhibition task, changes in neural activity were noted on fMRI when compared to the non-exposed subjects.⁸⁹ Although the exposed subjects committed more errors of commission, all were able to finish the task with 85% accuracy or more. While performing a visuospatial working memory task, the exposed subjects showed changes in neural activity on fMRI when compared to the nonexposed subjects although there was no group differences in performance.^{90,91}

Academic Achievement

Using tests, studies from the OPPS at ages 6 to 9 years⁹² and 13 to 16 years⁹³ showed no effect of prenatal marijuana exposure on standardized academic achievement test scores. This is in contrast to the findings from the MHPCD. Again, using standardized achievement tests, prenatally exposed children had lower reading, spelling and reading comprehension scores at age 10.⁹⁴ Similar results were found at age 14 with lower global achievement and reading scores in the prenatally exposed adolescents.⁹⁵

Behavior Problems

Parental reports for subjects in the OPPS showed increased conduct disorders in children from 6 to 9 years old.⁹² Parental and teacher reports obtained at age 10 for subjects in the MHPCD revealed increased delinquency and externalizing behaviors.⁹⁶ Also, an increase in self-reported depressive symptoms was identified at age 10 for exposed subjects in the MHPCD.⁹⁷ At age 14, the age of onset and frequency of the youth's marijuana use was predicted by their prenatal exposure.⁹⁸ This finding was also seen in 16- to 21-year-olds from the OPPS.⁹⁹ In this study, subjects who were prenatally exposed to marijuana were at greater risk for initiating cigarette smoking and daily use and for initiating marijuana use.

Cannabis microbiome sequencing reveals several mycotoxic fungi native to dispensary grade Cannabis flowers

McKernan K1, Spangler J1, Zhang L1, Tadigotla V1, Helbert Y1, Foss T1, Smith D1.

Medicinal Genomics Corporation, Woburn, MA, USA

Full text with 70 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4897766/>

The Center for Disease Control estimates 128,000 people in the U.S. are hospitalized annually due to food borne illnesses. This has created a demand for food safety testing targeting the detection of pathogenic mold and bacteria on agricultural products. This risk extends to medical Cannabis and is of particular concern with inhaled, vaporized and even concentrated Cannabis products . As a result, third party microbial testing has become a regulatory requirement in the medical and recreational Cannabis markets, yet knowledge of the Cannabis microbiome is limited. Here we describe the first next generation sequencing survey of the fungal communities found in dispensary based Cannabis flowers by ITS2 sequencing, and demonstrate the sensitive detection of several toxicogenic *Penicillium* and *Aspergillus* species, including *P. citrinum* and *P. paxilli*, that were not detected by one or more culture-based methods currently in use for safety testing.

Marijuana Strain And Pathogens • One Codex.com

Australian Bastard:

<https://app.onecodex.com/analysis/public/201e7f1642e04a3c>
<https://app.onecodex.com/analysis/public/58f1e03c10434bfa>

KD4:

<https://app.onecodex.com/analysis/public/2e86e262817246c4>
<https://app.onecodex.com/analysis/public/1abd5b60446140a0>

KD6:

<https://app.onecodex.com/analysis/public/a92d3dff5485499d>
<https://app.onecodex.com/analysis/public/8d72e2514e564ecd>

KD8:

<https://app.onecodex.com/analysis/public/8d72e2514e564ecd>
<https://app.onecodex.com/analysis/public/d6e2e0bcfba3469f>

Liberty Haze:

<https://app.onecodex.com/analysis/public/7bcd650fa5544f2c>
<https://app.onecodex.com/analysis/public/7f0feb6cb0a94d56>

Girls Scout Cookie:

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<https://app.onecodex.com/analysis/public/8d6f10c7ee684f93>

Jakes Grape:

<https://app.onecodex.com/analysis/public/bc8af5ed19e5407a>
<https://app.onecodex.com/analysis/public/99d7a4a2f7af486b>

RECON:

<https://app.onecodex.com/analysis/public/8a22a16cc2e24731>
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GreenCrack:

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Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood

Jacobus J1, Squeglia LM2, Meruelo AD3, Castro N3, Brumback T3, Giedd JN3, Tapert SF4.

1. Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA
University of California San Diego, Department of Psychiatry, La Jolla, CA, USA
2. Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, Charleston, SC, USA
3. University of California San Diego, Department of Psychiatry, La Jolla, CA, USA
4. Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA
University of California San Diego, Department of Psychiatry, La Jolla, CA, USA
Electronic address: stapert@ucsd.edu

Studies suggest marijuana impacts gray and white matter neural tissue development, however few prospective studies have determined the relationship between cortical thickness and cannabis use spanning adolescence to young adulthood. This study aimed to understand how heavy marijuana use influences cortical thickness trajectories across adolescence. Subjects were adolescents with heavy marijuana use and concomitant alcohol use (MJ+ALC, n=30) and controls (CON, n=38) with limited substance use histories. Participants underwent magnetic resonance imaging and comprehensive substance use assessment at three independent time points. Repeated measures analysis of covariance was used to look at main effects of group, time, and Group \times Time interactions on cortical thickness. MJ+ALC showed thicker cortical estimates across the brain (23 regions), particularly in frontal and parietal lobes ($p < .05$). More cumulative marijuana use was associated with increased thickness estimates by 3-year follow-up ($p < .05$). Heavy marijuana use during adolescence and into young adulthood may be associated with altered neural tissue development and interference with neuromaturation that can have neurobehavioral consequences. Continued follow-up of adolescent marijuana users will help understand ongoing neural changes that are associated with development of problematic use into adulthood, as well as potential for neural recovery with cessation of use.

Butane Hash Oil Burns Associated with Marijuana Liberalization in Colorado

Bell C1, Slim J2, Flaten HK3, Lindberg G1, Arek W1, Monte AA4,5,6.

1. University of Colorado Hospital Burn Center, Aurora, CO, USA
2. Denver Health Emergency Medicine Residency, Denver Health & Hospital Authority, Denver, CO, USA
3. University of Colorado Department of Emergency Medicine, Leprino Building, 7th Floor Campus Box B-215, 12401 E. 17th Avenue, Aurora, CO, 80045, USA
4. Denver Health Emergency Medicine Residency, Denver Health & Hospital Authority, Denver, CO, USA
5. University of Colorado Department of Emergency Medicine, Leprino Building, 7th Floor Campus Box B-215, 12401 E. 17th Avenue, Aurora, CO, 80045, USA
6. Rocky Mountain Poison & Drug Center, Denver, CO, USA
andrew.monte@ucdenver.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26289652>

Butane hash oil (BHO), also known as “amber,” “dab,” “glass,” “honey,” “shatter,” or “wax,” is a potent marijuana concentrate, containing up to 90 % tetrahydrocannabinol (THC). BHO is easily manufactured using highly volatile butane as a solvent. Our objective was to characterize hydrocarbon burns associated with BHO manufacture in Colorado. This was a cross-sectional study utilizing the National Burn Repository to capture all hydrocarbon burns reported to the local burn center from January 1st, 2008, through August 31st, 2014. We abstracted demographic and clinical variables from medical records for patients admitted for hydrocarbon burns associated with butane hash oil extraction. Twenty-nine cases of BHO burns were admitted to the local burn center during the study period. Zero cases presented prior to medical liberalization, 19 (61.3 %) during medical liberalization (Oct 2009-Dec 2013), and 12 (38.7 %) in 2014 since legalization. The majority of cases were Caucasian (72.4 %) males (89.7 %). Median age was 26 (range 15-58). The median total-body-surface-area (TBSA) burn size was 10 % (TBSA range 1-90 %). Median length of hospital admission was 10 days. Six required intubation for airway protection (21 %). Nineteen required skin grafting, eight wound care only, one required surgical fracture repair, and one required surgical debridement. Hydrocarbon burns associated with hash oil production have increased since the liberalization of marijuana policy in Colorado. A combination of public health messaging, standardization of manufacturing processes, and worker safety regulations are needed to decrease the risks associated with BHO production.

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Medicinal cannabis

By B. Murnion

Senior staff specialist, Drug Health Services, Royal Prince Alfred Hospital

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4674028/>

A number of therapeutic uses of cannabis and its derivatives have been postulated from preclinical investigations. Possible clinical indications include spasticity and pain in multiple sclerosis, cancer-associated nausea and vomiting, cancer pain and HIV neuropathy. However, evidence is limited, may reflect subjective rather than objective outcomes, and is not conclusive. Controversies lie in how to produce, supply and administer cannabinoid products. Introduction of cannabinoids therapeutically should be supported by a regulatory and educational framework that minimises the risk of harm to patients and the community. The Regulator of Medicinal Cannabis Bill 2014 is under consideration in Australia to address this. Nabiximols is the only cannabinoid on the Australian Register of Therapeutic Goods at present, although cannabidiol has been recommended for inclusion in Schedule 4.

Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies

de Carvalho MF1, Dourado MR2, Fernandes IB3, Araújo CT4, Mesquita AT5, Ramos-Jorge ML6.

1. Graduate Program in Dentistry Faculty of Sciences of Health, Federal University of Minas Gerais - UFMG, Av. Pres. Antônio Carlos, 6627 - Campus Pampulha CEP: 31.270-901, Belo Horizonte, MG, Brazil
2. Graduate Program in Oral Pathology, Piracicaba Dental School, University of Campinas - Unicamp, Av. Limeira, 901 - Vila Rezende, Piracicaba, SP 13414-903, Brazil
3. Graduate Program in Dentistry, Faculty of Sciences of Health, Federal University of Jequitinhonha and Mucuri Valleys - UFVJM, Rua da Glória, 187, Bairro Centro, CEP: 39.100-000, Diamantina, MG, Brazil
- 4,5. Department of Dentistry, Faculty of Sciences of Health, Federal University of Jequitinhonha and Mucuri Valleys - UFVJM, Rua da Glória, 187, Bairro Centro, CEP: 39.100-000, Diamantina, MG, Brazil
6. Department of Dentistry, Faculty of Sciences of Health, Federal University of Jequitinhonha and Mucuri Valleys - UFVJM, Rua da Glória, 187, Bairro Centro, CEP: 39.100-000, Diamantina, MG, Brazil

Electronic address: monize_c@hotmail.com

Electronic address: bellahfernandes@hotmail.com

Electronic address: mauricio_mrd@hotmail.com

Electronic address: ctpimenta@gmail.com.

Electronic address: hanamesquita@hotmail.com

Electronic address: mlramosjorge@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/26433192>

The scientific literature presents conflicting data on a possible causal relationship between marijuana users and the development of head and neck cancer.

No association between lifetime marijuana use and the development of head and neck cancer was found. The different methods of collection/presentation of results in the selected articles prevented other analyzes from being conducted. Additional studies are needed to assess for long-term effects.

Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)

Ware MA1, Wang T2, Shapiro S3, Collet JP4; COMPASS study team.
Boulanger A, Esdaile JM, Gordon A, Lynch M, Moulin DE, O'Connell C.

1. Department of Anesthesia, McGill University, Montreal, Quebec, Canada; Department of Family Medicine, McGill University, Montreal, Quebec, Canada
 2. Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
 3. Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada; Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada
 4. Department of Pediatrics, University of British Columbia; Child and Family Research Institute, Vancouver, British Columbia, Canada
- Electronic address: mark.ware@mcgill.ca

Full text, extensive, all inclusive report with graphs and charts and 19 references

<http://www.jpain.org/action/showFullTextImages?pii=S1526-5900%2815%2900837-8>

Cannabis is widely used as a self-management strategy by patients with a wide range of symptoms and diseases including chronic non-cancer pain. The safety of cannabis use for medical purposes has not been systematically evaluated. We conducted a prospective cohort study to describe safety issues among individuals with chronic non-cancer pain. A standardized herbal cannabis product (12.5% tetrahydrocannabinol) was dispensed to eligible individuals for a 1-year period; controls were individuals with chronic pain from the same clinics who were not cannabis users. The primary outcome consisted of serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Secondary efficacy parameters included pain and other symptoms, mood, and quality of life. Two hundred and fifteen individuals with chronic pain were recruited to the cannabis group (141 current users and 58 ex-users) and 216 controls (chronic pain but no current cannabis use) from 7 clinics across Canada. The median daily cannabis dose was 2.5 g/d. There was no difference in risk of serious adverse events (adjusted incidence rate ratio = 1.08, 95% confidence interval = .57-2.04) between groups. Medical cannabis users were at increased risk of non-serious adverse events (adjusted incidence rate ratio = 1.73, 95% confidence interval = 1.41-2.13); most were mild to moderate. There were no differences in secondary safety assessments. Quality-controlled herbal cannabis, when used by patients with experience of cannabis use as part of a monitored treatment program over 1 year, appears to have a reasonable safety profile. Longer-term monitoring for functional outcomes is needed.

This study evaluated the safety of cannabis use by patients with chronic pain over 1 year. The study found that there was a higher rate of adverse events among cannabis users compared with controls but not for serious adverse events at an average dose of 2.5 g herbal cannabis per day.

Polypharmacology Shakes Hands with Complex Aetiopathology

Brodie JS1, Di Marzo V2, Guy GW1.

1. GW Pharmaceuticals plc, Sovereign House, Vision Park, Histon, Cambridge, CB24 9BZ, UK

2. Endocannabinoid Research Group, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, Comprensorio Olivetti, 80078, Pozzuoli (NA), Italy

Electronic address: vdimarzo@icb.cnr.it

<http://www.ncbi.nlm.nih.gov/pubmed/26434643>

Chronic diseases are due to deviations of fundamental physiological systems, with different pathologies being characterised by similar malfunctioning biological networks. The ensuing compensatory mechanisms may weaken the body's dynamic ability to respond to further insults and reduce the efficacy of conventional single target treatments. The multitarget, systemic, and prohomeostatic actions emerging for plant cannabinoids exemplify what might be needed for future medicines. Indeed, two combined cannabis extracts were approved as a single medicine (Sativex[®]), while pure cannabidiol, a multitarget cannabinoid, is emerging as a treatment for paediatric drug-resistant epilepsy. Using emerging cannabinoid medicines as an example, we revisit the concept of polypharmacology and describe a new empirical model, the 'therapeutic handshake', to predict efficacy/safety of compound combinations of either natural or synthetic origin.

Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure

Watson CT^{1,2}, Szutorisz H¹, Garg P², Martin Q², Landry JA², Sharp AJ², Hurd YL^{1,3}.

1. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
2. Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA
3. Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26044905>

Drug exposure during critical periods of development is known to have lasting effects, increasing one's risk for developing mental health disorders. Emerging evidence has also indicated the possibility for drug exposure to even impact subsequent generations. Our previous work demonstrated that adolescent exposure to $\Delta(9)$ -tetrahydrocannabinol (THC), the main psychoactive component of marijuana (*Cannabis sativa*), in a Long-Evans rat model affects reward-related behavior and gene regulation in the subsequent (F1) generation unexposed to the drug. Questions, however, remained regarding potential epigenetic consequences. In the current study, using the same rat model, we employed Enhanced Reduced Representation Bisulfite Sequencing to interrogate the epigenome of the nucleus accumbens, a key brain area involved in reward processing. This analysis compared 16 animals with parental THC exposure and 16 without to characterize relevant systems-level changes in DNA methylation. We identified 1027 differentially methylated regions (DMRs) associated with parental THC exposure in F1 adults, each represented by multiple CpGs. These DMRs fell predominantly within introns, exons, and intergenic intervals, while showing a significant depletion in gene promoters. From these, we identified a network of DMR-associated genes involved in glutamatergic synaptic regulation, which also exhibited altered mRNA expression in the nucleus accumbens. These data provide novel insight into drug-related cross-generational epigenetic effects, and serve as a useful resource for investigators to explore novel neurobiological systems underlying drug abuse vulnerability.

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An animal model of female adolescent cannabinoid exposure elicits a long-lasting deficit in presynaptic long-term plasticity

Lovelace JW1, Corches A2, Vieira PA1, Hiroto AS1, Mackie K3, Korzus E4.

1. Department of Psychology & Neuroscience Program, University of California Riverside, CA 92521, USA
2. Biomedical Sciences Program, University of California Riverside, CA 92521, USA
3. Department of Psychological & Brain Sciences, Gill Center for Biomedical Sciences, Indiana University, Bloomington, IN 47405, USA
4. Department of Psychology & Neuroscience Program, University of California Riverside, CA 92521, USA
Biomedical Sciences Program, University of California Riverside, CA 92521, USA
Electronic address: edkorzus@ucr.edu

<http://www.ncbi.nlm.nih.gov/pubmed/25979486>

Cannabis continues to be the most accessible and popular illicit recreational drug. Whereas current data link adolescence cannabinoid exposure to increased risk for dependence on other drugs, depression, anxiety disorders and psychosis, the mechanism(s) underlying these adverse effects remains controversial. The observed deficit in cortical presynaptic signaling may represent a neural maladaptation underlying network instability and abnormal cognitive functioning.

Our study suggests that adolescent cannabinoid exposure may permanently impair brain functions, including the brain's intrinsic ability to appropriately adapt to external influences.

Preliminary findings demonstrating latent effects of early adolescent marijuana use onset on cortical architecture

Filbey FM1, McQueeney T2, DeWitt SJ2, Mishra V3.

1,2. Center for BrainHealth, School of Behavioral and Brain Sciences, The University of Texas at Dallas, USA

3. Advance MRI, LLC, Frisco, TX, USA

Electronic address: Francesca.Filbey@utdallas.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26507433>

As the most commonly used illicit substance during early adolescence, long-term or latent effects of early adolescent marijuana use across adolescent developmental processes remain to be determined.

We examined cortical thickness, gray/white matter border contrast (GWR) and local gyrification index (LGI) in 42 marijuana (MJ) users. Voxelwise regressions assessed early-onset (age <16) vs. late-onset (≥ 16 years-old) differences and relationships to continued use while controlling for current age and alcohol use.

Divergent patterns between current MJ use and elements of cortical architecture were associated with early MJ use onset. Considering brain development in early adolescence, findings are consistent with disruptions in pruning. However, divergence with continued use for many years thereafter suggests altered trajectories of brain maturation during late adolescence and beyond.

The impact of initiation: Early onset marijuana smokers demonstrate altered Stroop performance and brain activation

Sagar KA1, Dahlgren MK2, Gönenç A3, Racine MT4, Dreman MW5, Gruber SA6.

1,2,3,4,5. Cognitive and Clinical Neuroimaging Core, McLean Imaging Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

6. Cognitive and Clinical Neuroimaging Core, McLean Imaging Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

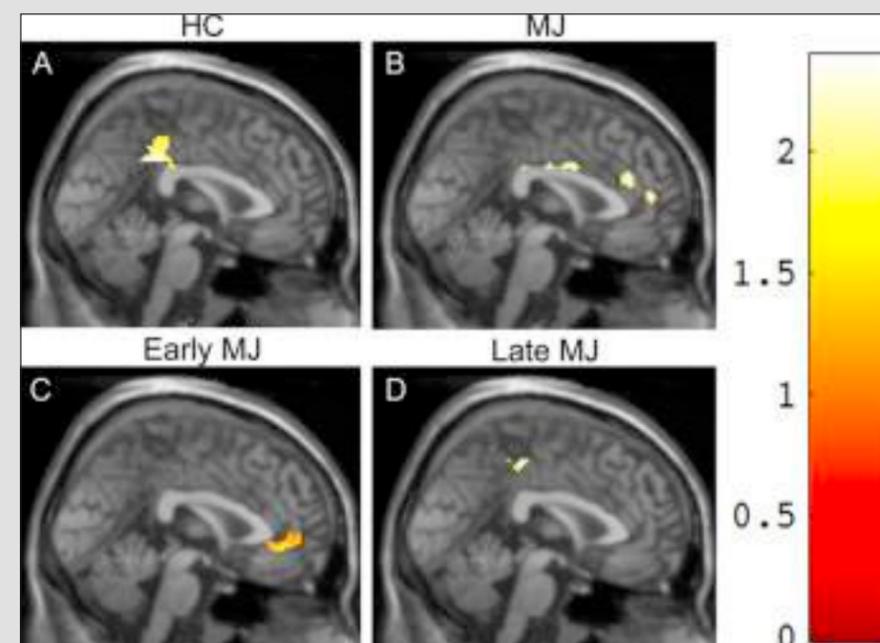
Department of Psychiatry, Harvard Medical School, Boston, MA 02215, United States

Electronic address: ksagar@mcean.harvard.edu

Full text with 68 references

<http://www.sciencedirect.com/science/article/pii/S1878929315000407>

Marijuana (MJ) use is on the rise, particularly among teens and emerging adults. This poses serious public health concern, given the potential deleterious effects of MJ on the developing brain. We examined 50 chronic MJ smokers divided into early onset (regular MJ use prior to age 16; n=24) and late onset (age 16 or later; n=26), and 34 healthy control participants (HCs). All completed a modified Stroop Color Word Test during fMRI. Results demonstrated that MJ smokers exhibited significantly poorer performance on the Interference subtest of the Stroop, as well as altered patterns of activation in the cingulate cortex relative to HCs. Further, early onset MJ smokers exhibited significantly poorer performance relative to both HCs and late onset smokers. Additionally, earlier age of MJ onset as well as increased frequency and magnitude (grams/week) of MJ use were predictive of poorer Stroop performance. fMRI results revealed that while late onset smokers demonstrated a more similar pattern of activation to the control group, a different pattern was evident in the early onset group. These findings underscore the importance of assessing age of onset and patterns of MJ use and support the need for widespread education and intervention efforts among youth.



Stroop (interference-rest/fixation)-(color naming-rest/fixation) fMRI activation: single-group comparison. Single-group comparisons on the Stroop Interference condition: HCs (A) demonstrated robust posterior activation in the right cingulate, while MJ smokers (B) exhibited more diffuse activation throughout the cingulate. Within MJ smokers, the early onset group (C) demonstrated activation in the anterior region of the cingulate, adjacent to the genu of the corpus callosum, whereas late onset smokers (D) exhibited posterior activation in the right cingulate, more similar to the HC group.

Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

Smith LA1, Azariah F, Lavender VT, Stoner NS, Bettiol S.

Department of Psychology, Social Work and Public Health, Oxford Brookes University, Jack Straws Lane, Marston, Oxford, UK

<http://www.ncbi.nlm.nih.gov/pubmed/26561338>

Cannabis has a long history of medicinal use. Cannabis-based medications (cannabinoids) are based on its active element, delta-9-tetrahydrocannabinol (THC), and have been approved for medical purposes. Cannabinoids may be a useful therapeutic option for people with chemotherapy-induced nausea and vomiting that respond poorly to commonly used anti-emetic agents (anti-sickness drugs). However, unpleasant adverse effects may limit their widespread use.

Cannabis-based medications may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, methodological limitations of the trials limit our conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions.

Epilepsy Behavior • November 2015

Issues and promise in clinical studies of botanicals with anticonvulsant potential

By D. Ekstein

Department of Neurology, Agnes Ginges Center of Neurogenetics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
Electronic address: dekstein@hadassah.org.il

<http://www.ncbi.nlm.nih.gov/pubmed/26341963>

Botanicals are increasingly used by people with epilepsy worldwide. However, despite abundant preclinical data on the anticonvulsant properties of many herbal remedies, there are very few human studies assessing safety and efficacy of these products in epilepsy. Additionally, the methodology of most of these studies only marginally meets the requirements of evidence-based medicine. Although the currently available evidence for the use of cannabinoids in epilepsy is similarly lacking, several carefully designed and well controlled industry-sponsored clinical trials of cannabis derivatives are planned to be completed in the next couple of years, providing the needed reliable data for the use of these products. The choice of the best botanical candidates with anticonvulsant properties and their assessment in well-designed clinical trials may significantly improve our ability to effectively and safely treat patients with epilepsy. This article is part of a Special Issue entitled "Botanicals for Epilepsy".

BMC Cancer • November 2015

Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis

Gurney J1, Shaw C2, Stanley J3, Signal V4, Sarfati D4.

1,2,3,4. Department of Public Health, University of Otago, PO Box 7343, Wellington, New Zealand

jason.gurney@otago.ac.nz.

caroline.shaw@otago.ac.nz.

james.stanley@otago.ac.nz.

virginia.signal@otago.ac.nz.

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4642772/>

The aetiology of testicular cancer remains elusive. In this manuscript, we review the evidence regarding the association between cannabis use and testicular cancer development. Using meta-analysis techniques, we observed that a) current, b) chronic, and c) frequent cannabis use is associated with the development of TGCT, when compared to never-use of the drug. The strongest association was found for non-seminoma development--for example, those using cannabis on at least a weekly basis had two and a half times greater odds of developing a non-seminoma TGCT compared those who never used cannabis. We found inconclusive evidence regarding the relationship between cannabis use and the development of seminoma tumours. It must be noted that these observations were derived from three studies all conducted in the United States; and the majority of data collection occurred during the 1990's.

“Wild cannabis”: A review of the traditional use and phytochemistry of *Leonotis leonurus*

Nsuala BN1, Enslin G2, Viljoen A3.

1,2,3. Department of Pharmaceutical Sciences, Faculty of Science, Tshwane University of Technology, Private Bag X680, Pretoria, 0001, South Africa
SAMRC Herbal Drugs Research Unit, Faculty of Science, Tshwane University of Technology, Private Bag X680, Pretoria, 0001, South Africa
Electronic address: enslingm@tut.ac.za

<http://www.ncbi.nlm.nih.gov/pubmed/26292023>

Leonotis leonurus, locally commonly known as “wilde dagga” (=wild cannabis), is traditionally used as a decoction, both topically and orally, in the treatment of a wide variety of conditions such as haemorrhoids, eczema, skin rashes, boils, itching, muscular cramps, headache, epilepsy, chest infections, constipation, spider and snake bites. The dried leaves and flowers are also smoked to relieve epilepsy. The leaves and flowers are reported to produce a mild euphoric effect when smoked and have been said to have a similar, although less potent, psychoactive effect to cannabis.

Despite the publication of various papers on *L. leonurus*, there is still, however, the need for definitive research and clarification of other compounds, including alkaloids and essential oils from *L. leonurus*, as well as from other plant parts, such as the roots which are extensively used in traditional medicine. The traditional use by smoking also requires further investigation as to how the chemistry and activity are affected by this form of administration. Research has proven the psychoactive effects of the crude extract of *L. leonurus*, but confirmation of the presence of psychoactive compounds, as well as isolation and characterization, is still required. Deliberate adulteration of *L. leonurus* with synthetic cannabinoids has been reported recently, in an attempt to facilitate the marketing of these illegal substances, highlighting the necessity for refinement of appropriate quality control processes to ensure safety and quality. Much work is therefore still required on the aspect of quality control to ensure safety, quality and efficacy of the product supplied to patients, as this plant is widely used in South Africa as a traditional medicine. Commercially available plant sources provide a viable option for phytochemical research, particularly with regard to the appropriate validation of the plant material (taxonomy) in order to identify and delimit closely related species such as *L. leonurus* and *L. nepetifolia* which are very similar in habit.

Prenatal exposure to cannabinoids evokes long-lasting functional alterations by targeting CB1 receptors on developing cortical neurons

de Salas-Quiroga A1, Díaz-Alonso J1, García-Rincón D1, Remmers F2, Vega D3, Gómez-Cañas M4, Lutz B2, Guzmán M1, Galve-Roperh I5.

1. Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), 28049 Madrid, Spain
Instituto de Investigación Sanitaria Ramón y Cajal (IRYCIS), 28034 Madrid, Spain
Department of Biochemistry and Molecular Biology I, Complutense University, 28040 Madrid, Spain
2. Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University Mainz, 55128 Mainz, Germany
3. Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), 28049 Madrid, Spain
Department of Biochemistry and Molecular Biology I, Complutense University, 28040 Madrid, Spain
4. Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), 28049 Madrid, Spain
Instituto de Investigación Sanitaria Ramón y Cajal (IRYCIS), 28034 Madrid, Spain; Department of Biochemistry and Molecular Biology III, Complutense University, 28040 Madrid, Spain
5. Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), 28049 Madrid, Spain
Instituto de Investigación Sanitaria Ramón y Cajal (IRYCIS), 28034 Madrid, Spain
Department of Biochemistry and Molecular Biology I, Complutense University, 28040 Madrid, Spain
igr@quim.ucm.es

Full text with 39 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640742/>

The CB1 cannabinoid receptor, the main target of $\Delta(9)$ -tetrahydrocannabinol (THC), the most prominent psychoactive compound of marijuana, plays a crucial regulatory role in brain development as evidenced by the neurodevelopmental consequences of its manipulation in animal models. Likewise, recreational cannabis use during pregnancy affects brain structure and function of the progeny. However, the precise neurobiological substrates underlying the consequences of prenatal THC exposure remain unknown. As CB1 signaling is known to modulate long-range corticofugal connectivity, we analyzed the impact of THC exposure on cortical projection neuron development. THC administration to pregnant mice in a restricted time window interfered with subcerebral projection neuron generation, thereby altering corticospinal connectivity, and produced long-lasting alterations in the fine motor performance of the adult offspring. Consequences of THC exposure were reminiscent of those elicited by CB1 receptor genetic ablation, and CB1-null mice were resistant to THC-induced alterations. The identity of embryonic THC neuronal targets was determined by a Cre-mediated, lineage-specific, CB1 expression-rescue strategy in a CB1-null background. Early and selective CB1 reexpression in dorsal telencephalic glutamatergic neurons but not forebrain GABAergic neurons rescued the deficits in corticospinal motor neuron development of CB1-null mice and restored susceptibility to THC-induced motor alterations. In addition, THC administration induced an increase in seizure susceptibility that was mediated by its interference with CB1-dependent regulation of both glutamatergic and GABAergic neuron development. These findings demonstrate that prenatal exposure to THC has long-lasting deleterious consequences in the adult offspring solely mediated by its ability to disrupt the neurodevelopmental role of CB1 signaling.

Vaping cannabis (marijuana): parallel concerns to e-cigs?

Budney AJ1, Sargent JD1, Lee DC1.

1. Geisel School of Medicine at Dartmouth, Hanover, NH, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26264448>

The proliferation of vaporization ('vaping') as a method for administering cannabis raises many of the same public health issues being debated and investigated in relation to e-cigarettes (e-cigs). Good epidemiological data on the prevalence of vaping cannabis are not yet available, but with current trends towards societal approval of medicinal and recreational use of cannabis, the pros and cons of vaping cannabis warrant study. As with e-cigs, vaping cannabis portends putative health benefits by reducing harm from ingesting toxic smoke. Indeed, vaping is perceived and being sold as a safer way to use cannabis, despite the lack of data on the health effects of chronic vaping. Other perceived benefits include better taste, more efficient and intense effects and greater discretion which allows for use in more places. Unfortunately, these aspects of vaping could prompt an increased likelihood of trying cannabis, earlier age of onset, more positive initial experiences, and more frequent use, thereby increasing the probability of problematic use or addiction. Sales and marketing of vaping devices with no regulatory guidelines, especially related to advertising or product development targeting youth, parallels concerns under debate related to e-cigs and youth. Thus, the quandary of whether or not to promote vaping as a safer method of cannabis administration for those wishing to use cannabis, and how to regulate vaping and vaping devices, necessitates substantial investigation and discussion. Addressing these issues in concert with efforts directed towards e-cigs may save time and energy and result in a more comprehensive and effective public health policy on vaping.

Cannabis Liberalization and Adolescent Cannabis Use: A Cross-National Study in 38 Countries

Shi Y1, Lenzi M2, An R3.

Full text with 47 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4659554/>

To assess the associations between types of cannabis control policies at country level and prevalence of adolescent cannabis use.

Multilevel logistic regressions were performed on 172,894 adolescents 15 year of age who participated in the 2001/2002, 2005/2006, or 2009/2010 cross-sectional Health Behaviour in School-Aged Children (HBSC) survey in 38 European and North American countries. Self-reported cannabis use status was classified into ever use in life time, use in past year, and regular use. Country-level cannabis control policies were categorized into a dichotomous measure (whether or not liberalized) as well as 4 detailed types (full prohibition, depenalization, decriminalization, and partial prohibition). Control variables included individual-level sociodemographic characteristics and country-level economic characteristics. Considerable intra-class correlations (.15-.19) were found at country level. With respect to the dichotomized cannabis control policy, adolescents were more likely to ever use cannabis (odds ratio (OR) = 1.10, $p = .001$), use in past year (OR = 1.09, $p = .007$), and use regularly (OR = 1.26, $p = .004$). Although boys were substantially more likely to use cannabis, the correlation between cannabis liberalization and cannabis use was smaller in boys than in girls. With respect to detailed types of policies, depenalization was associated with higher odds of past-year use (OR = 1.14, $p = .013$) and regular use (OR = 1.23, $p = .038$), and partial prohibition was associated with higher odds of regular use (OR = 2.39, $p = .016$). The correlation between cannabis liberalization and regular use was only significant after the policy had been introduced for more than 5 years.

Cannabis liberalization with depenalization and partial prohibition policies was associated with higher levels of regular cannabis use among adolescents. The correlations were heterogeneous between genders and between short- and long-terms.

The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review

Boyчук DG, Goddard G, Mauro G, Orellana MF.

<http://www.ncbi.nlm.nih.gov/pubmed/25635955>

To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain.

Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta- 9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events. Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.

Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery.

HU-444, a Novel, Potent Anti-Inflammatory, Nonpsychotropic Cannabinoid

Haj CG1, Sumariwalla PF1, Hanuš L1, Kogan NM1, Yektin Z1, Mechoulam R2, Feldmann M1, Gallily R2.

1,2. Institute for Drug Research (C.G.H., L.H., N.M.K., R.M.) and Lautenberg Center for Immunology (Z.Y., R.G.), Hebrew University Medical Faculty, Jerusalem, Israel
Kennedy Institute of Rheumatology, Hammersmith, London, United Kingdom (P.F.S., M.F.)
mechou@cc.huji.ac.il and ruthg@ekmd.huji.ac.il

<http://www.ncbi.nlm.nih.gov/pubmed/26272937>

Cannabidiol (CBD) is a component of cannabis, which does not cause the typical marijuana-type effects, but has a high potential for use in several therapeutic areas. In contrast to $\Delta(9)$ -tetrahydrocannabinol ($\Delta(9)$ -THC), it binds very weakly to the CB1 and CB2 cannabinoid receptors. It has potent activity in both in vitro and in vivo anti-inflammatory assays. Thus, it lowers the formation of tumor necrosis factor (TNF)- α , a proinflammatory cytokine, and was found to be an oral antiarthritic therapeutic in murine collagen-induced arthritis in vivo. However, in acidic media, it can cyclize to the psychoactive $\Delta(9)$ -THC. We report the synthesis of a novel CBD derivative, HU-444, which cannot be converted by acid cyclization into a $\Delta(9)$ -THC-like compound. In vitro HU-444 had anti-inflammatory activity (decrease of reactive oxygen intermediates and inhibition of TNF- α production by macrophages); in vivo it led to suppression of production of TNF- α and amelioration of liver damage as well as lowering of mouse collagen-induced arthritis. HU-444 did not cause $\Delta(9)$ -THC-like effects in mice. We believe that HU-444 represents a potential novel drug for rheumatoid arthritis and other inflammatory diseases.

Journal Of Addiction • October 2015

The Cannabis Dilemma: A Review of Its Associated Risks and Clinical Efficacy

Zhang MW1, Ho RC2.

1. National Addiction Management Service, Institute of Mental Health, Singapore 539747
2. Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119054

Full text with 52 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619948/>

Cannabis, also known as marijuana, has 9-tetrahydrocannabinol as the main constituent. There has been strict legislation governing the utilization of cannabis locally and worldwide. However, there has been an increasing push to make cannabis legalized, in view of its potential medical and therapeutic effects, for various medical disorders ranging from development disorders to cancer treatment, and being an adjunctive medication for various neurological conditions. It is the aim of this review paper to explore the evidence base for its proposed therapeutic efficacy and to compare the evidence base supporting its proposed therapeutic efficacy with its known and well-researched medical and psychiatric side effects.

Marijuana Use in Epilepsy: The Myth and the Reality

Detyniecki K1, Hirsch L.

1. Yale Comprehensive Epilepsy Center, Department of Neurology, Yale University, 15 York Street, LCI 7, New Haven, CT, 06520, USA
kamil.detyniecki@yale.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26299273>

Marijuana has been utilized as a medicinal plant to treat a variety of conditions for nearly five millennia. Over the past few years, there has been an unprecedented interest in using cannabis extracts to treat epilepsy, spurred on by a few refractory pediatric cases featured in the media that had an almost miraculous response to cannabidiol-enriched marijuana extracts. This review attempts to answer the most important questions a clinician may have regarding the use of marijuana in epilepsy. First, we review the preclinical and human evidences for the anticonvulsant properties of the different cannabinoids, mainly tetrahydrocannabinol (THC) and cannabidiol (CBD). Then, we explore the safety data from animal and human studies. Lastly, we attempt to reconcile the controversy regarding physicians' and patients' opinions about whether the available evidence is sufficient to recommend the use of marijuana to treat epilepsy.

Neurotherapeutics • October 2015

Cannabinoids and Epilepsy

Rosenberg EC1, Tsien RW1, Whalley BJ2, Devinsky O3.

1. Department of Neuroscience and Physiology, Neuroscience Institute, NYU Langone Medical Center, New York, NY, 10016, USA
2. School of Pharmacy, The University of Reading, Whiteknights, Reading, RG6 6AP, UK
3. Department of Neurology, Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY, 10016, UK
od4@nyu.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26282273>

Cannabis has been used for centuries to treat seizures. Recent anecdotal reports, accumulating animal model data, and mechanistic insights have raised interest in cannabis-based antiepileptic therapies. In this study, we review current understanding of the endocannabinoid system, characterize the pro- and anticonvulsive effects of cannabinoids [e.g., Δ 9-tetrahydrocannabinol and cannabidiol (CBD)], and highlight scientific evidence from pre-clinical and clinical trials of cannabinoids in epilepsy. These studies suggest that CBD avoids the psychoactive effects of the endocannabinoid system to provide a well-tolerated, promising therapeutic for the treatment of seizures, while whole-plant cannabis can both contribute to and reduce seizures. Finally, we discuss results from a new multicenter, open-label study using CBD in a population with treatment-resistant epilepsy. In all, we seek to evaluate our current understanding of cannabinoids in epilepsy and guide future basic science and clinical studies.

Neurotherapeutics • October 2015

Cannabinoids and Schizophrenia: Risks and Therapeutic Potential

Manseau MW1, Goff DC2.

1,2. Department of Psychiatry, New York University Langone Medical Center, New York, NY, USA.
Donald.Goff@nyumc.org

<http://www.ncbi.nlm.nih.gov/pubmed/26311150>

A convergence of evidence shows that use of *Cannabis sativa* is associated with increased risk of developing psychotic disorders, including schizophrenia, and earlier age at which psychotic symptoms first manifest. Cannabis exposure during adolescence is most strongly associated with the onset of psychosis amongst those who are particularly vulnerable, such as those who have been exposed to child abuse and those with family histories of schizophrenia. Schizophrenia that develops after cannabis use may have a unique clinical phenotype, and several genetic polymorphisms may modulate the relationship between cannabis use and psychosis. The endocannabinoid system has been implicated in psychosis both related and unrelated to cannabis exposure, and studying this system holds potential to increase understanding of the pathophysiology of schizophrenia. Anandamide signaling in the central nervous system may be particularly important. $\Delta(9)$ -Tetrahydrocannabinol in cannabis can cause symptoms of schizophrenia when acutely administered, and cannabidiol (CBD), another compound in cannabis, can counter many of these effects. CBD may have therapeutic potential for the treatment of psychosis following cannabis use, as well as schizophrenia, possibly with better tolerability than current antipsychotic treatments. CBD may also have anti-inflammatory and neuroprotective properties. Establishing the role of CBD and other CBD-based compounds in treating psychotic disorders will require further human research.

Systematic Review of the Use of Phytochemicals for Management of Pain in Cancer Therapy

Harrison AM1, Heritier F2, Childs BG3, Bostwick JM4, Dziadzko MA5.

1. Medical Scientist Training Program, Mayo Clinic, Rochester, MN 55905, USA
2. Department of Anesthesiology, CH du Forez, 42600 Montbrison, France
3. Mayo Graduate School, Mayo Clinic, Rochester, MN 55905, USA
4. Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN 55905, USA
5. Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905, USA

Full text with 48 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630373/>

Pain in cancer therapy is a common condition and there is a need for new options in therapeutic management. While phytochemicals have been proposed as one pain management solution, knowledge of their utility is limited. The objective of this study was to perform a systematic review of the biomedical literature for the use of phytochemicals for management of cancer therapy pain in human subjects. Of an initial database search of 1,603 abstracts, 32 full-text articles were eligible for further assessment. Only 7 of these articles met all inclusion criteria for this systematic review. The average relative risk of phytochemical versus control was 1.03 [95% CI 0.59 to 2.06]. In other words (although not statistically significant), patients treated with phytochemicals were slightly more likely than patients treated with control to obtain successful management of pain in cancer therapy. We identified a lack of quality research literature on this subject and thus were unable to demonstrate a clear therapeutic benefit for either general or specific use of phytochemicals in the management of cancer pain. This lack of data is especially apparent for psychotropic phytochemicals, such as the Cannabis plant (marijuana). Additional implications of our findings are also explored.

Cortical thinness and volume differences associated with marijuana abuse in emerging adults

Mashhoon Y1, Sava S2, Sneider JT3, Nickerson LD4, Silveri MM3.

1. Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Belmont, MA, USA
McLean Imaging Center, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA, USA
2. Neurodevelopmental Laboratory on Addictions and Mental Health, McLean Hospital, Belmont, MA, USA
Department of Psychiatry, Harvard Medical School, Boston, MA, USA
Boston VA Healthcare System, Brockton, MA, USA, Harvard South Shore Residency Program, Brockton, MA, USA
3. Neurodevelopmental Laboratory on Addictions and Mental Health, McLean Hospital, Belmont, MA, USA
McLean Imaging Center, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA, USA
4. Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Belmont, MA, USA
McLean Imaging Center, McLean Hospital, Belmont, MA, USA, Department of Psychiatry, Harvard Medical School, Boston, MA, USA
Electronic address: ymashhoon@mclean.harvard.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26249265>

The prevalence of marijuana (MJ) use among youth and its legalization for medical or recreational use has intensified public health endeavors of understanding MJ effects on brain structure and function. Studies indicate that MJ use is related to impaired cognitive performance, and altered functional brain activation and chemistry in adolescents and adults, but MJ effects on brain morphology in emerging adults are less understood.

Right fusiform gyrus cortical thinness and smaller thalamic volume in emerging adults is associated with marijuana abuse. Furthermore, smaller thalamic volume associated with greater impulsivity contributes to growing evidence that the thalamus is neurobiologically perturbed by marijuana use. Collectively, altered thalamic and right fusiform gyrus structural integrity may interfere with their known roles in regulating visuoperceptual and object information processing.

Alteration of delta-6-desaturase (FADS2), secretory phospholipase-A2 (sPLA2) enzymes by Hot-nature diet with co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients

Rezapour-Firouzi S1, Arefhosseini SR2, Ebrahimi-Mamaghani M3, Baradaran B4, Sadeghihokmabad E5, Mostafaei S6, Torbati M7, Chehreh M8.

1. Neurosciences Research Center, University of Medical Sciences at Tabriz, Iran
School of Nutrition and Health, University of Medical Sciences at Tabriz, Iran
Department of Immunology, Microbiology and Genetics, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
2. School of Nutrition and Health, University of Medical Sciences at Tabriz, Iran
Nutrition Research Center, University of Medical Sciences at Tabriz, Iran
3. School of Nutrition and Health, University of Medical Sciences at Tabriz, Iran
4. Immunology Research Center, University of Medical Sciences at Tabriz, Iran
5. Neurosciences Research Center, University of Medical Sciences at Tabriz, Iran
6. Neurosciences Research Center, University of Medical Sciences at Tabriz, Iran
7. Department of Food Science and Technology Faculty of Nutrition, Food & Drug Organization, University of Medical Sciences at Tabriz, Iran
8. Islamic Azad University, Tabriz, Iran

Electronic address: s.firozi@gmail.com.

Electronic address: arefhosseinir@tbzmed.ac.ir.

Electronic address: ebrahimamagani@tbzmed.ac.ir

Electronic address: Behzad_im@yahoo.com.

Electronic address: aeass@yahoo.com

Electronic address: somaiyehmostafaei@yahoo.com

Electronic address: drtorbati@yahoo.com

Electronic address: mchehreh@yahoo.com

<http://www.ncbi.nlm.nih.gov/pubmed/26365444>

The effect of nutrition and dietary supplements as environmental factors has been suggested as possible factors affecting both disease risk and progression in on the course of multiple sclerosis with complex genetic-risk profiles. This study was aimed to assess regulation of surface-membrane enzymes such as Delta-6-desaturase (FADS2), secretory Phospholipase A2(sPLA2) by hemp seed and evening primrose oils as well as Hot-natured dietary intervention in relapsing remitting multiple sclerosis (RRMS) patients.

The co-supplemented hemp seed and evening primrose oils with Hot nature diet can have beneficial effects in improving clinical symptoms and signs in relapsing remitting multiple sclerosis patients which were confirmed by regulation of surface-membrane enzymes.

“Time for dabs”: Analyzing Twitter data on marijuana concentrates across the U.S

Daniulaityte R1, Nahhas RW2, Wijeratne S3, Carlson RG4, Lamy FR4, Martins SS5, Boyer EW6, Smith GA3, Sheth A3.

1. Center for Interventions, Treatment, and Addictions Research (CITAR), Department of Community Health, Wright State University Boonshoft School of Medicine, Dayton, OH, USA
2. Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, Dayton, OH, USA
Department of Psychiatry, Wright State University Boonshoft School of Medicine, Dayton, OH, USA
3. Ohio Center of Excellence in Knowledge-enabled Computing (Kno.e.sis), Department of Computer Science and Engineering, Wright State University, Dayton, OH, USA
4. Center for Interventions, Treatment, and Addictions Research (CITAR), Department of Community Health, Wright State University Boonshoft School of Medicine, Dayton, OH, USA
5. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA
6. Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, MA, USA

Electronic address: raminta.daniulaityte@wright.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/26338481>

Media reports suggest increasing popularity of marijuana concentrates (“dabs”; “earwax”; “budder”; “shatter”; “butane hash oil”) that are typically vaporized and inhaled via a bong, vaporizer or electronic cigarette. However, data on the epidemiology of marijuana concentrate use remain limited. This study aims to explore Twitter data on marijuana concentrate use in the U.S. and identify differences across regions of the country with varying cannabis legalization policies.

Tweets were collected between October 20 and December 20, 2014, using Twitter’s streaming API. Twitter data filtering framework was available through the eDrugTrends platform. Raw and adjusted percentages of dabs-related tweets per state were calculated. A permutation test was used to examine differences in the adjusted percentages of dabs-related tweets among U.S. states with different cannabis legalization policies.

eDrugTrends collected a total of 125,255 tweets. Almost 22% (n=27,018) of these tweets contained identifiable state-level geolocation information. Dabs-related tweet volume for each state was adjusted using a general sample of tweets to account for different levels of overall tweeting activity for each state. Adjusted percentages of dabs-related tweets were highest in states that allowed recreational and/or medicinal cannabis use and lowest in states that have not passed medical cannabis use laws. The differences were statistically significant.

Twitter data suggest greater popularity of dabs in the states that legalized recreational and/or medical use of cannabis. The study provides new information on the epidemiology of marijuana concentrate use and contributes to the emerging field of social media analysis for drug abuse research.

Translational Pediatrics • October 2015

Cannabinoids for pediatric epilepsy? Up in smoke or real science?

By F. M. Filloux

Division of Pediatric Neurology, University of Utah School of Medicine and Primary Children's Hospital, Division of Pediatric Neurology, Salt Lake City, USA

Full text with 66 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729003/>

Public interest in the use of “medical marijuana” for the treatment of childhood epilepsy has burgeoned in the last few years. This has occurred in parallel with a growing interest in “medical marijuana” in general. Physicians and pediatricians must balance their patients’ desire for immediate access to these products with the tenets of evidence-based medicine. This review discusses the biochemistry of cannabis products (the phytocannabinoids) setting this in the context of the endogenous endocannabinoid system. The differing and potentially modulating effects of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are reviewed. The evidence-base supporting or not the use of cannabis products for the treatment of neurological disease and specifically epilepsy is explored. The potential for adverse effects and particularly of neurotoxicity is addressed. Finally, public health and sociocultural implications are touched upon. Specific recommendations for interested physicians are provided including advocacy for patients and for a change in the “scheduling” of cannabis in order to better foster much-needed high-quality scientific research in this important area.

Momentum grows for medical use of cannabis

By Chris McCall

An American girl whose life might have been saved by cannabis has inspired a surge of interest in cannabis-derived medications, which scientists say is long overdue. Chris McCall reports.

Charlotte Figi is now 7 years old and she has only just started school, but she is also internationally famous. Charlotte, from Colorado Springs, CO, USA, has the rare genetic condition Dravet syndrome and was not expected to live when her mother began treating her with cannabis in 2011. "We were dealing with 50 seizures a day, two an hour. She could not walk. She could not swallow", her mother Paige Figi told *The Lancet*. "I started digging around. You are just watching your little baby girl die. I thought there has to be something to do for this poor kid."

Since Paige started treating Charlotte with an laboratory-tested oil (given under the tongue, in a measured amount) derived from a specific, unusual strain of cannabis, the improvement has been remarkable. Publicity about the case has helped prompt a string of US states to legalise marijuana for medical purposes. Charlotte will never live an ordinary life, but she can talk with the aid of a computer and no longer needs a feeding tube.

The Figi family's story has inspired thousands of other concerned parents, and has led to renewed pressure for laws on marijuana to be eased around the world. However, alongside the lobby for medical marijuana is a parallel lobby for legal recreational marijuana, and often the same people are pushing for both. Colorado, where the Figi family live, last year became the first US state to legalise the drug for recreational use. By next year, at least four US states will have done so. Last week, Australia announced that it would amend its drug laws to allow for cannabis to be legally grown for medical and scientific purposes.

With more than 20 000 medical users in Canada, more than 20 000 in Israel, and would-be users lining up around the world, medical marijuana looks set to stay. But doctors, pharmacologists, and other scientists say there are thorny issues over legal inconsistencies, lack of a solid evidence base, quality of the drug, and the fact that it is the only medicinal drug which can be smoked.

Perhaps the most thorny, however, and the most hotly debated, is the link between cannabis and schizophrenia, particularly in young users. Although the evidence is disputed, there is little doubt that at least some recreational users are at higher risk of developing psychotic illness.

Cannabis sativa originated in Asia and spread around the world, partly because as hemp it was a good source of strong fibre for ropes on sailing ships, very flexible, and resistant to rot. It has also historically been used as a medicine for numerous disorders. Cannabis is a dioecious plant, meaning male and female flowers are found on separate plants. It is around the female flowers that concentrations of the chemicals known as cannabinoids are found, leading smokers of marijuana to favour the female flowers, which have the greatest psychoactive properties. In nature, these substances seem to play a part in protecting the flowers from certain insects. They are only found in the cannabis plant.

In a parallel with the opium poppy, which gave the world morphine in the 19th century, cannabinoids interact with receptors found in the nervous system of mammals. The science of this is well established and is not in dispute. However, the illegal status of cannabis has hindered research, says Jonathan Page, a plant biologist at the University of British Columbia, Canada, who has recently mapped the *C sativa* genome. "There is still a lot to be learned and to be discovered about this plant. Even getting samples of cannabis materials

into a university lab is still very challenging”, he said.

The best known of the cannabinoids is tetrahydrocannabinol (THC), which is responsible for the high that smokers of cannabis seek. Over decades, marijuana growers have selectively bred plants greater and greater in concentrations of THC. Many modern plants contain several times more THC than in their ancestors. Pure THC is a clear oil and is a partial agonist of the receptors of the analogous human system. The second most abundant cannabinoid, cannabidiol, is less known. Referred to as CBD, it lacks psychoactive effects. In its pure form, it is a white powder, and as an antagonist, it has pharmacological effects that are largely opposite to THC.

The entire endogenous endocannabinoid system seems to be a modulator of the nervous system, operating in the synapses of nerves and regulating nervous activity. This property gives it wide-ranging effects, potentially making it a source for many clinically useful drugs. Apart from controlling seizures, potential and actual medical uses include treating Crohn’s disease and other inflammatory conditions of the gut because of its anti-inflammatory properties, alleviating chronic pain in palliative care, preventing graft-versus-host disease in transplant patients, and even treating psychosis.

In Charlotte Figi’s case, it was a strain of cannabis high in CBD and low in THC that controlled her seizures. Her mother Paige, who once did a pre-med course although she never trained as a doctor, says she discovered anecdotal accounts of cannabis being used to treat epilepsy dating back as far as the 18th century and devised her own informal tests with the help of a local marijuana grower in Colorado, to work out how much to give her daughter. Interestingly, plants high in THC made Charlotte’s seizures worse.

Israeli chemist Raphael Mechoulam, who discovered THC in 1964, says the flood of interest in cannabis-derived medications should have happened long ago. Evidence for effectiveness of CBD for seizures was obtained decades ago. “It is overdue. There is no doubt that cannabinoids from the plant

and the equivalent molecules in the brain, which were discovered many years later, are of extreme interest”, he said, citing as an example the use of cannabinoids for intractable pain in palliative care. “Pain is like an emotion and they seem to block the negative aspects of pain. People sometimes tell me ‘I still feel the pain but I don’t mind the pain’.

Mechoulam said his own past studies were also hampered by legal restrictions. In one case, police supplied seized Lebanese hashish for research purposes, but the subsequent trials had to be done in South America, with a researcher in São Paulo taking a lead role.

Trials in severe paediatric epilepsy, chemotherapy-induced nausea and vomiting, and symptom relief in terminal illness have started this year in Australia. In Colorado, US\$9 million accumulated by the state as a result of medicinal cannabis sales over 15 years has been assigned to studies, including for inflammatory bowel disease, post-traumatic stress disorder, and sleep. British drug firm GW Pharmaceuticals is another organisation that is undertaking trials testing the use of cannabis derivatives in diabetes and schizophrenia among other disorders.

How do you know which type of cannabis to use for a given condition? How do you know it is safe? Ryan Vandrey, a behavioural pharmacologist at Johns Hopkins University, MD, USA, says the answer is robust clinical trials and probably billions of dollars in research. At present, users of medicinal marijuana are running substantial risks, partly because of the lack of evidence. “People who smoke it can have a miserable time. That is going to be different from one person to the next and there is no way to predict ahead of time whether you are going to have a bad time. A lot of the side-effects are dose dependent”, he said. “You don’t have any of that science to really back up [medical use]. I would envisage that this is something that develops over decades.”

The end result may be cannabis-derived drugs that go through a period on patent, during which they will be quite expensive, he says, and not quite the

cheap cure-all that many proponents imagine. In the end, though, doctors and pharmacists will be able to say with some confidence how these drugs work. Already some such drugs are on the market, such as Sativex (nabiximols), a mouth spray containing THC and CBD now marketed in some countries to relieve spasticity in multiple sclerosis.

Larry Wolk, a paediatrician who heads Colorado's public health division, says that initial data suggest that the negative effects from legalising marijuana for recreational use have not been as catastrophic as feared, although there has been a mild increase in emergency department admissions related to marijuana and at least one death related to edible marijuana.

Colorado's legalisation of recreational marijuana still involves some restrictions. Advertising is not permitted and only people older than 21 years can register as a recreational user, although younger people can potentially receive it for medical purposes. The people supplying both forms of marijuana are often the same. "If you are there for medical you turn to the left, if you are there for personal you turn to the right", Wolk said.

Psychiatrist Michael Bostwick of the Mayo Clinic, MN, USA, is sceptical about medical marijuana, and says the current methods for prescribing cannabis in the USA involve some questionable practices. A US medical practitioner's licence is a federal licence and the federal government still lists cannabis and its main derivatives as schedule 1 drugs—meaning by definition that they have no medical use. Even if some states have legalised marijuana, the federal law has not changed. In reality, Bostwick says, prescriptions for cannabis in the USA are frequently not being issued directly by doctors, who would be taking a big personal risk. "They run the risk of losing their federal licence", he said.



Charlotte Figi and her father at a cannabis greenhouse in Colorado Springs

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)00674-1/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00674-1/fulltext)

Current Pain Headache Reports • October 2015

Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence

Jensen B1, Chen J, Furnish T, Wallace M.

Center for Pain Medicine, University of California San Diego, 9300 Campus Point Drive, Mail Code 7651, La Jolla, CA, 92037, USA
bbjensen@ucsd.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26325482>

Cannabinoid compounds include phytocannabinoids, endocannabinoids, and synthetics. The two primary phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with CB1 receptors in the brain and peripheral tissue and CB2 receptors in the immune and hematopoietic systems. The route of delivery of cannabis is important as the bioavailability and metabolism are very different for smoking versus oral/sublingual routes. Gold standard clinical trials are limited; however, some studies have thus far shown evidence to support the use of cannabinoids for some cancer, neuropathic, spasticity, acute pain, and chronic pain conditions.

Cannabinoids and Tremor Induced by Motor-related Disorders: Friend or Foe?

Arjmand S1, Vaziri Z1, Behzadi M1, Abbassian H1, Stephens GJ2, Shabani M3.

1. Kerman Neuroscience Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran
2. School of Pharmacy, University of Reading, Whiteknights, P.O. Box 228, Reading, RG6 6AJ, UK
3. Kerman Neuroscience Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran
shabani@kmu.ac.ir

<http://www.ncbi.nlm.nih.gov/pubmed/26152606>

Tremor arises from an involuntary, rhythmic muscle contraction/relaxation cycle and is a common disabling symptom of many motor-related diseases such as Parkinson disease, multiple sclerosis, Huntington disease, and forms of ataxia. In the wake of anecdotal, largely uncontrolled, observations claiming the amelioration of some symptoms among cannabis smokers, and the high density of cannabinoid receptors in the areas responsible for motor function, including basal ganglia and cerebellum, many researchers have pursued the question of whether cannabinoid-based compounds could be used therapeutically to alleviate tremor associated with central nervous system diseases. In this review, we focus on possible effects of cannabinoid-based medicines, in particular on Parkinsonian and multiple sclerosis-related tremors and the common probable molecular mechanisms. While, at present, inconclusive results have been obtained, future investigations should extend preclinical studies with different cannabinoids to controlled clinical trials to determine potential benefits in tremor.

High School Students' Use of Electronic Cigarettes to Vaporize Cannabis

Morean ME1, Kong G2, Camenga DR3, Cavallo DA2, Krishnan-Sarin S2.

1. Department of Psychology, Oberlin College, Oberlin, Ohio
2. Department of Psychiatry, and
3. Department of Emergency Medicine, Yale University School of Medicine, New Haven, Connecticut
meghan.morean@gmail.com.

<http://www.ncbi.nlm.nih.gov/pubmed/26347431>

Electronic cigarette (e-cigarette) use is increasing rapidly among high school (HS) students. Of concern, e-cigarettes can be used to vaporize cannabis, although use rates among adolescents are unknown. We evaluated lifetime rates of using e-cigarettes to vaporize cannabis among all lifetime e-cigarette users (27.9%), all lifetime cannabis users (29.2%), and lifetime users of both e-cigarettes and cannabis (18.8%); common means of vaporizing cannabis including hash oil, wax infused with Δ -9-tetrahydrocannabinol (THC), and dried cannabis; and demographic predictors of using e-cigarettes to vaporize cannabis.

In the spring of 2014, 3,847 Connecticut HS students completed an anonymous survey assessing e-cigarette and cannabis use.

Vaporizing cannabis using e-cigarettes was common among lifetime e-cigarette users, lifetime cannabis users, and lifetime dual users (e-cigarette 18.0%, cannabis 18.4%, dual users 26.5%). Students reported using e-cigarettes to vaporize hash oil (e-cigarette 15.4%, cannabis 15.5%, dual users 22.9%) and wax infused with THC (e-cigarette 10.0%, cannabis 10.2%, dual users 14.8%) and using portable electronic vaporizers to vaporize dried cannabis leaves (e-cigarette 19.6%, lifetime cannabis 23.1%, lifetime dual users 29.1%). Binary logistic regression indicated that male students (odds ratio [OR] = 2.05), younger students (OR = 0.64), lifetime e-cigarette users (OR = 5.27), and lifetime cannabis users (OR = 40.89) were most likely to vaporize cannabis using e-cigarettes. Rates also differed by HS attended.

Rates of vaporizing cannabis using e-cigarettes were high. These findings raise concerns about the lack of e-cigarette regulations and the potential use of e-cigarettes for purposes other than vaping nicotine.

Concomitant discovery of lung cancer and tuberculosis in a cannabis smoker

Cadelis G1, Ehret N2.

1,2. Service de pneumologie, CHU de Pointe-à-Pitre, 97159 Pointe-à-Pitre cedex, Guadeloupe
Electronic address: gilbert.cadelis@chu-guadeloupe.fr.

<http://www.ncbi.nlm.nih.gov/pubmed/25725601>

The coexistence of lung cancer and active tuberculosis is relatively rare. We report a case of concomitant discovery of lung cancer and tuberculosis in the context of addiction to tobacco and cannabis.

A 50-year-old man, smoking tobacco and cannabis since the age of 18, was hospitalized for hemoptysis. Physical examination revealed cachexia, hyperthermia and decreased breath sounds on auscultation of the left lung field. The chest X-ray objectified atelectasis of the left upper lobe. The CT scan revealed a left upper lobe atelectasis and a cavity surrounded opacities taking a tree in bud appearance located at the apex of the left lower lobe. Endoscopy showed an obstruction by a bud located at the upper left lobe. Histology of bronchial biopsy revealed squamous cell carcinoma. Direct examination of bacteriological samples found BAAR and culture confirmed tuberculosis. The contamination could occur via a close relative, smoking cannabis and being treated for tuberculosis. After a 6-month treatment for tuberculosis, the patient underwent a course of chemotherapy, but refused further treatment. Death occurred 3 months later.

This observation relates the concomitant discovery of lung cancer and tuberculosis. It also highlights the possible role of cannabis addiction in the transmission of tuberculosis and the occurrence of lung cancer in combination with tobacco.

Cannabidiol as a Potential Treatment for Anxiety Disorders

Blessing EM1, Steenkamp MM2, Manzanares J2,3, Marmar CR2.

1. New York University School of Medicine, New York, NY, USA

2. New York University School of Medicine, New York, NY, USA

3. Instituto de Neurociencias de Alicante, Universidad Miguel Hernández and Consejo Superior de Investigaciones Científicas, Alicante, Spain
esther.blessing@nyumc.org

<http://www.ncbi.nlm.nih.gov/pubmed/26341731>

Cannabidiol (CBD), a *Cannabis sativa* constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

**Public opinion and medical cannabis policies:
examining the role of underlying beliefs and national medical cannabis policies**

Sznitman SR1, Bretteville-Jensen AL2.

1. School of Public Health, University of Haifa, Eshkol Tower, room 705, Mt. Carmel, 3190501, Haifa, Israel
2. Norwegian Institute for Alcohol and Drug Research, Post Box 565, Sentrum, 0105, Oslo, Norway
sznitman@research.haifa.ac.il.

Full text with 50 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4606899/>

Debate about medical cannabis legalization are typically informed by three beliefs: (1) cannabis has medical effects, (2) medical cannabis is addictive and (3) medical cannabis legalization leads to increased used of cannabis for recreational purposes (spillover effects). We examined how strongly these beliefs are associated with public support for medical cannabis legalization and whether this association differs across divergent medical cannabis policy regimes.

The belief that cannabis has medical benefits is particularly salient for support for medical cannabis legalization. It is possible that the recent surge in evidence supporting the medical benefits of cannabis will increase the belief about medical benefits of cannabis in the general population which may in turn increase public support for medical cannabis legalization. Results also suggest that once medical cannabis is legalized, factors beyond cannabis-specific beliefs will increasingly influence medical cannabis legalization support. These conclusions are, however, only suggestive as the current study is based on cross-sectional data. Hopefully, future research will be able to capitalize on changes in medical cannabis policies and conduct longitudinal studies that enable an examination of the causal relation between public opinion and medical cannabis policy changes.

Examining the relationship between the physical availability of medical marijuana and marijuana use across fifty California cities

Bridget Freisthler and Paul J. Gruenewald

Bridget Freisthler, UCLA Department of Social Welfare, 3250 Public Affairs Building, Box 951656, Los Angeles, CA, USA

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161654/>

The purpose of the current study is to assess statistical associations between individual demographic and personality characteristics, the city-level physical availability of medical marijuana (as measured through densities per roadway mile of storefront dispensaries and delivery services), and the incidence and prevalence of marijuana use.

Individual level data on marijuana use were collected during a telephone survey of 8,853 respondents living in 50 mid-size cities in California. Data on medical marijuana dispensaries and delivery services were obtained via six different websites and official city lists. Three outcome variables pertaining to lifetime, past year use, and frequency of past year use were analyzed using random effects logistic models (for lifetime and past year use) and random effects tobit models (for frequency of past 365-day use).

The current study finds that the total physical availability of medical marijuana through dispensaries and delivery services per roadway mile at the city-level is positively related to current marijuana use and greater frequency of use, controlling for a variety of demographic and personality characteristics. As expected, current physical availability of medical marijuana was unrelated to lifetime use.

Regulations on the number and densities of marijuana outlets may be a sufficient means to restrain overall levels of marijuana use within cities. However, alternative use of delivery services may also provide easy access to marijuana and mitigate these effects.

Neurotherapeutics • October 2015

Clinical Use of Cannabinoids for Symptom Control in Multiple Sclerosis

By W.G. Notcutt

Department of Pain Management, James Paget University Hospital, Great Yarmouth, Norfolk, NR31 6LA, UK
willnotcutt@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/26289248>

The endocannabinoid system was discovered in 1988 but has received little attention for its potential therapeutic possibilities. That has started to change, and since 2000, a significant number of clinical trials of cannabinoids, principally for the control of spasticity in multiple sclerosis, have been undertaken. These studies have been difficult because of the nature of the disease and have involved patients for whom other therapies have failed or proved inadequate. This paper outlines the background to the use of cannabinoids available and discusses the principles of practice associated with their safe use. The focus has been on nabiximols, being the most studied and the only cannabinoid that has been both adequately researched for use in multiple sclerosis and granted a license by the regulators. However, what has emerged is that the effect for many patients can be much wider than just control of spasticity. Within and outside of neurology there seems to be an expanding range of possibilities for the therapeutic use of cannabinoids.

**No smoke, no fire:
What the initial literature suggests regarding vapourized cannabis and respiratory risk**

Loflin M1, Earleywine M1.

Author information

Habits and Lifestyles Laboratory, Department of Psychology, University at Albany, State University of New York, Albany, New York, USA

Full text with 20 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4456813/>

As more municipalities relax restrictions on access to cannabis, questions about the plant's potential for respiratory effects become more common. Given current limitations in developing an inhalant alternative for delivering cannabis medication, smoked marijuana remains the most readily accessible form of cannabis among medicinal users (1). An important question that remains is how to improve safety for the respiratory system in individuals who choose to use cannabis medicinally. Although frequent comparisons with tobacco emphasize that the smoke from cannabis has more carcinogens and respiratory irritants, the absence of nicotine likely mitigates the impact of some of these compounds (2). Evidence suggesting a link between cannabis and lung cancer is equivocal (2–4), but other concerns remain important. Frequent smokers of cannabis often report respiratory problems. Many users experience symptoms of bronchitis including coughing, wheezing and tightness in the chest (5,6). Informed health care professionals may consider making recommendations to their medicinal cannabis patients for vapourization of the plant, particularly for those who want the rapid relief that oral administration fails to provide. It is not our intention to encourage inappropriate use of the plant, but to increase safety for those who choose to use it. Vapourization of cannabis is likely less harmful than smoking. Nevertheless, researchers have yet to gather some of the most necessary data regarding the topic. There have been no published randomized clinical trials investigating vapourization with long-term follow-up; therefore, drawing firm conclusions about the impact of the technique is difficult. Preliminary findings do support the idea that vapourization is an improvement over smoking.

NATURE • September 2015

Drug development: The treasure chest

By Brian Owens

Brian Owens is a freelance science writer based in St. Stephen, New Brunswick

Pharmaceutical research into the chemicals found in cannabis has so far supplied only one licensed medicine.
But scientists think there could be hundreds more.

http://www.nature.com/nature/journal/v525/n7570_supp/full/525S6a.html

NATURE • September 2015

A potted history

By Stephanie Pain

For thousands of years cannabis has been valued as a versatile herbal medicine.
In the twentieth century, prescription gave way to proscription.
Might this ancient remedy be about to regain its healing reputation?

http://www.nature.com/nature/journal/v525/n7570_supp/full/525S10a.html

NATURE • September 2015

Medical marijuana: Showdown at the cannabis corral

By Michael Eisenstein

Researchers are gathering clinical data for medical marijuana
against a backdrop of deregulation and opportunism.

http://www.nature.com/nature/journal/v525/n7570_supp/full/525S15a.html

Marijuana for Glaucoma: A Recipe for Disaster or Treatment?

Sun X1, Xu CS2, Chadha N3, Chen A1, Liu J2.

1. Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey, Pennsylvania
2. Department of Ophthalmology and Visual Science, Yale School of Medicine, New Haven, Connecticut
3. Icahn School of Medicine at Mount Sinai/New York Eye and Ear Infirmary of Mount Sinai, New York, NY

Full text with 43 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4553646/>

Marijuana has been shown to lower intraocular pressure (IOP) but with limited duration of action and numerous adverse effects. Use of marijuana to lower IOP as a means of glaucoma treatment would require frequent use throughout the day, leading to significant adverse effects, possible progression toward Cannabis Use Disorder (CUD), and/or withdrawal symptoms. The treatment of glaucoma based on the cannabis plant or drugs based on the cannabinoid molecule should be considered carefully before being prescribed. Considerations should include the adverse physical and psychological adverse effects, including substance abuse. Currently, the deleterious effects of marijuana outweigh the benefits of its IOP-lowering capacity in most glaucoma patients. Under extremely rare circumstances, a few categories of glaucoma patients may be potential candidates for treatment with medical marijuana. Further studies on alternate routes and more focused means of cannabinoid molecule delivery to the eye for glaucoma treatment are needed.

Medical Marijuana: More Questions than Answers

By Kevin P. Hill, M.D., M.H.S

Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, Massachusetts Harvard Medical School, Boston, Massachusetts, USA

Full text with 15 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4243838/>

With 23 states and the District of Columbia having enacted medical marijuana laws as of August 2014, it is important that psychiatrists be able to address questions about medical marijuana from patients, families, and other health care professionals. The author discusses the limited medical literature on synthetic cannabinoids and medical marijuana. The synthetic cannabinoids dronabinol and nabilone are approved by the United States Food and Drug Administration for nausea and vomiting associated with cancer chemotherapy and appetite stimulation in patients with wasting diseases such as acquired immunodeficiency syndrome (AIDS). Results of clinical trials of these agents for other conditions have varied widely thus far. In addition, few data are available on the use of the marijuana plant as a medical treatment. The author concludes that there is a clear need for additional research on possible medical uses of cannabinoids. He notes that discussions with prospective medical marijuana patients should emphasize the importance of communication among all parties due to the possible side effects of treatment with marijuana and its potential to interact with other medications the patient may be taking. Facilitating a thorough substance abuse consultation is one of most positive ways that psychiatrists, especially addiction psychiatrists, can make an impact as medical marijuana becomes increasingly common. A careful review of the prospective medical marijuana user's substance use history, co-occurring medical and psychiatric conditions, family history, and psychosocial stressors is essential in evaluating the potential risks of medical marijuana for these patients. The author concludes that psychiatrists can have a significant impact by increasing the likelihood that medical marijuana will be used in a safe and responsible way.

Medical marijuana is here to stay. Despite strong science demonstrating the potential dangers of regular marijuana use and the absence of endorsement of medical marijuana by any major medical organization,^{1,2} Pandora's Box is now open. As of August 2014, residents of 23 states and the District of Columbia have voted to enact medical marijuana laws.³ As medical marijuana is implemented, the controversy surrounding the topic has fostered considerable uncertainty. A heated debate on the merits of the legalization of marijuana is ongoing as well, with both Colorado and Washington State legalizing the recreational use of marijuana. It is important, therefore, for psychiatrists to ask a number of key questions and be prepared to address those questions when raised by patients, families, and other health care professionals in states with medical marijuana.

Nonsmoker Exposure to Secondhand Cannabis Smoke. III. Oral Fluid and Blood Drug Concentrations and Corresponding Subjective Effects

Cone EJ1, Bigelow GE2, Herrmann ES2, Mitchell JM3, LoDico C4, Flegel R4, Vandrey R2.

1,2. Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, Baltimore, MD, USA

3. RTI International, Research Triangle Park, NC, USA

4. Division of Workplace Programs (DWP), Substance Abuse and Mental Health Services Administration (SAMHSA), Rockville, MD, USA
edwardjcone@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/26139312>

The increasing use of highly potent strains of cannabis prompted this new evaluation of human toxicology and subjective effects following passive exposure to cannabis smoke. The study was designed to produce extreme cannabis smoke exposure conditions tolerable to drug-free nonsmokers. Six experienced cannabis users smoked cannabis cigarettes [5.3% $\Delta(9)$ -tetrahydrocannabinol (THC) in Session 1 and 11.3% THC in Sessions 2 and 3] in a closed chamber. Six nonsmokers were seated alternately with smokers during exposure sessions of 1 h duration. Sessions 1 and 2 were conducted with no ventilation and ventilation was employed in Session 3. Oral fluid, whole blood and subjective effect measures were obtained before and at multiple time points after each session. Oral fluid was analyzed by ELISA (4 ng/mL cutoff concentration) and by LC-MS-MS (limit of quantitation) for THC (1 ng/mL) and total THCCOOH (0.02 ng/mL). Blood was analyzed by LC-MS-MS (0.5 ng/mL) for THC, 11-OH-THC and free THCCOOH. Positive tests for THC in oral fluid and blood were obtained for nonsmokers up to 3 h following exposure. Ratings of subjective effects correlated with the degree of exposure. Subjective effect measures and amounts of THC absorbed by nonsmokers (relative to smokers) indicated that extreme secondhand cannabis smoke exposure mimicked, though to a lesser extent, active cannabis smoking.

Psychology Of Addictive Behaviors • September 2015

Variability in Medical Marijuana Laws in the United States

¹Jessica Bestrashniy and Ken C. Winters

1. Department of Mathematics, St. Olaf College, Northfield, MN, USA

Full text with 8 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588056/>

Marijuana use and its distribution raise several complex health, social and legal issues in the United States. Marijuana is prohibited in only 23 states and pro-marijuana laws are likely to be introduced in these states in the future. Increased access to and legalization of medical marijuana may have an impact on recreational marijuana use and perception through increased availability and decreased restrictiveness around the drug. The authors undertook an analysis to characterize the policy features of medical marijuana legislation, including an emphasis on the types of medical conditions that are included in medical marijuana laws. A high degree of variability in terms of allowable medical conditions, limits on cultivation and possession, and restrictiveness of policies was discovered. Further research is needed to determine if this variability impacts recreational use in those states.

Chest • September 2015

Cannabis Smoking in 2015: A Concern for Lung Health?

Biehl JR, Burnham EL.

<http://www.ncbi.nlm.nih.gov/pubmed/25996274>

Recent legislative successes allowing expanded access to recreational and medicinal cannabis have been associated with its increased use by the public, despite continued debates regarding its safety within the medical and scientific communities. Despite legislative changes, cannabis is most commonly used by smoking, although alternatives to inhalation have also emerged. Moreover, the composition of commercially available cannabis has dramatically changed in recent years. Therefore, developing sound scientific information regarding its impact on lung health is imperative, particularly because published data conducted prior to widespread legalization are conflicting and inconclusive. In this commentary, we delineate major observations of epidemiologic investigations examining cannabis use and the potential associated development of airways disease and lung cancer to highlight gaps in pulmonary knowledge. Additionally, we review major histopathologic alterations related to smoked cannabis and define specific areas in animal models and human clinical translational investigations that could benefit from additional development. Given that cannabis has an ongoing classification as a schedule 1 medication, federal funding to support investigations of modern cannabis use in terms of medicinal efficacy and safety profile on lung health have been elusive. It is clear, however, that the effects of inhaled cannabis on lung health remain uncertain and given increasing use patterns, are worthy of further investigation.

The academic consequences of marijuana use during college

Arria AM1, Caldeira KM1, Bugbee BA1, Vincent KB1, O'Grady KE2.

1. University of Maryland School of Public Health
2. University of Maryland

<http://www.ncbi.nlm.nih.gov/pubmed/26237288>

Although several studies have shown that marijuana use can adversely affect academic achievement among adolescents, less research has focused on its impact on postsecondary educational outcomes. This study utilized data from a large longitudinal cohort study of college students to test the direct and indirect effects of marijuana use on college grade point average (GPA) and time to graduation, with skipping class as a mediator of these outcomes. A structural equation model was evaluated taking into account a variety of baseline risk and protective factors (i.e., demographics, college engagement, psychological functioning, alcohol and other drug use) thought to contribute to college academic outcomes. The results showed a significant path from baseline marijuana use frequency to skipping more classes at baseline to lower first-semester GPA to longer time to graduation. Baseline measures of other drug use and alcohol quantity exhibited similar indirect effects on GPA and graduation time. Over time, the rate of change in marijuana use was negatively associated with rate of change in GPA, but did not account for any additional variance in graduation time. Percentage of classes skipped was negatively associated with GPA at baseline and over time. Thus, even accounting for demographics and other factors, marijuana use adversely affected college academic outcomes, both directly and indirectly through poorer class attendance. Results extend prior research by showing that marijuana use during college can be a barrier to academic achievement. Prevention and early intervention might be important components of a comprehensive strategy for promoting postsecondary academic achievement.

Use and effects of cannabinoids in military veterans with posttraumatic stress disorder

Betthausen K1, Pilz J1, Vollmer LE2.

1. Kevin Betthausen, Pharm.D., is Postgraduate Year 1 (PGY1) Pharmacy Resident, Barnes-Jewish Hospital, St. Louis, MO, USA
Jeffrey Pilz, Pharm.D., is PGY1 and 2-Master of Science in Health-System Pharmacy Administration Resident, University of Kansas Hospital, Kansas City, KS, USA
Laura E. Vollmer, Pharm.D., is PGY1 Pharmacy Resident, University of Minnesota Medical Center, Minneapolis, MN, USA
 2. Kevin Betthausen, Pharm.D., is Postgraduate Year 1 (PGY1) Pharmacy Resident, Barnes-Jewish Hospital, St. Louis, MO, USA
Jeffrey Pilz, Pharm.D., is PGY1 and 2-Master of Science in Health-System Pharmacy Administration Resident, University of Kansas Hospital, Kansas City, KS, USA
Laura E. Vollmer, Pharm.D., is PGY1 Pharmacy Resident, University of Minnesota Medical Center, Minneapolis, MN, USA
- At the time of writing, all authors were Pharm.D. students, College of Pharmacy and Health Sciences, Drake University, Des Moines, IA, USA
laura.vollmer@drake.edu

<http://www.ncbi.nlm.nih.gov/pubmed/26195653>

Published evidence regarding the use of cannabis and cannabis derivatives by military veterans with posttraumatic stress disorder (PTSD) is reviewed.

When inhaled or delivered orally or transdermally, cannabinoids (the psychoactive components of unrefined marijuana and various derivative products) activate endogenous cannabinoid receptors, modulating neurotransmitter release and producing a wide range of central nervous system effects, including increased pleasure and alteration of memory processes. Those effects provide a pharmacologic rationale for the use of cannabinoids to manage the three core PTSD symptom clusters: reexperiencing, avoidance and numbing, and hyperarousal. A literature search identified 11 articles pertaining to cannabis use by military veterans who met standard diagnostic criteria for PTSD. Cross-sectional studies have found a direct correlation between more severe PTSD symptomatology and increased motivation to use cannabis for coping purposes, especially among patients with difficulties in emotional regulation or stress tolerance. Data from 4 small studies suggested that cannabinoid use was associated with global improvements in PTSD symptoms or amelioration of specific PTSD symptoms such as insomnia and nightmares. Large well-designed controlled trials are needed in order to better delineate the potential role of cannabinoids as an adjunct or alternative to conventional approaches to PTSD management.

While further research into cannabinoid treatment effects on PTSD symptoms is required, the evaluated evidence indicates that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety and insomnia and improved coping ability.

Cannabis smoke can be a major risk factor for early-age laryngeal cancer— a molecular signaling-based approach

Bhattacharyya S1, Mandal S, Banerjee S, Mandal GK, Bhowmick AK, Murmu N.

Department of Signal Transduction and Biogenic Amines, Chittaranjan National Cancer Institute, 37-S.P Mukherjee Road, Kolkata, 700026, India

<http://www.ncbi.nlm.nih.gov/pubmed/25736926>

Epidermal growth factor receptor (EGFR) and its downstream elements are overexpressed in most cases of the head and neck squamous cell carcinoma. This study investigated the expression pattern of key proteins linked to the EGFR pathway in laryngeal carcinoma patients with a history of cannabis smoking. We selected 83 male glottic cancer patients, aged between 45 to 75 years with three distinct populations-nonsmoker, cigarette smoker, and cannabis smoker. Immunohistochemical staining was performed for EGFR, protein kinase B (PKB or Akt), nuclear factor kappa B p50 (NF- κ B), and cyclooxygenase-2 (COX-2) followed by boolean scoring for statistical analysis. Experimental data showed upregulation of the selected EGFR cascade in tumor cells, stromal expression of EGFR, and nuclear localization of COX-2 in metaplastic gland cells of laryngeal cancer tissue sample. Statistical analyses indicated that overexpression of the EGFR cascade is significantly correlated to cannabis smoking. Cannabis smokers had higher expression ($p < 0.01$) of these oncoproteins with respect to both nonsmokers as well as cigarette smokers. Risk factor analysis showed high risk of these proteins expression in age < 60 years (odds ratio (OR) > 1.5) as the lower age group had relatively higher number of cannabis smokers. This study provides evidence for a direct association between cannabis smoking and increased risk of laryngeal cancer. Higher expression of the EGFR cascade in cannabis smokers revealed that cannabis smoking may be a major cause for the early onset of aggressive laryngeal cancer.

Pharmacy Students' Knowledge and Attitudes Regarding Medical Marijuana

Karen E. Moeller, PharmD and Barbara Woods, MA, RPh

University of Kansas, Lawrence, Kansas

Full text with 28 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4584377/>

To determine pharmacy students' knowledge of and attitudes toward medical marijuana and to determine if pharmacy students need additional education on the topic.

Pharmacy students were asked to complete a survey on medical marijuana that assessed their knowledge of, medical uses of, adverse effects with, and attitudes toward medical marijuana through 23 Likert-scale questions.

Three hundred eleven students completed the survey. Fifty-eight percent of the students felt that medical marijuana should be legalized in all states. However, the majority of students did not feel comfortable answering consumers' questions regarding efficacy, safety, or drug interactions related to the substance. Accurate responses for diseases or conditions for permitted medical marijuana use was low, with only cancer (91%) and glaucoma (57%) identified by more than half the students.

With an increasing number of states adopting medical marijuana use, pharmacy schools need to evaluate the adequacy of medical marijuana education in their curriculum.

Efficacy and adverse effects of medical marijuana for chronic noncancer pain

Systematic review of randomized controlled trials

Amol Deshpande, MD MBA, Consultant physician in the Comprehensive Pain Program
of the University Health Network in Toronto, Ontario, Canada

Angela Mailis-Gagnon, MSc MD FRCPC, Medical Director of the Comprehensive Pain Program
and Professor in the Faculty of Medicine at the University of Toronto, Canada

Nivan Zoheiry, MD PhD, Research analyst in the Comprehensive Pain Program, Canada

Shehnaz Fatima Lakha, Research assistant in the Comprehensive Pain Program
and is a doctoral candidate in the Institute of Medical Sciences at the University of Toronto, Canada

Full text with 26 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4541447/>

To determine if medical marijuana provides pain relief for patients with chronic noncancer pain (CNCP) and to determine the therapeutic dose, adverse effects, and specific indications.

In April 2014, MEDLINE and EMBASE searches were conducted using the terms chronic noncancer pain, smoked marijuana or cannabinoids, placebo and pain relief, or side effects or adverse events. An article was selected for inclusion if it evaluated the effect of smoked or vaporized cannabinoids (nonsynthetic) for CNCP; it was designed as a controlled study involving a comparison group, either concurrently or historically; and it was published in English in a peer-review journal. Outcome data on pain, function, dose, and adverse effects were collected, if available. All articles that were only available in abstract form were excluded. A total of 6 randomized controlled trials (N = 226 patients) were included in this review; 5 of them assessed the use of medical marijuana in neuropathic pain as an adjunct to other concomitant analgesics including opioids and anticonvulsants. The 5 trials were considered to be of high quality; however, all of them had challenges with masking. Data could not be pooled owing to heterogeneity in delta-9-tetrahydrocannabinol potency by dried weight, differing frequency and duration of treatment, and variability in assessing outcomes. All experimental sessions in the studies were of short duration (maximum of 5 days) and reported statistically significant pain relief with nonserious side effects.

There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of delta-9-tetrahydrocannabinol, and lack of functional outcomes. Although well tolerated in the short term, the long-term effects of psychoactive and neurocognitive effects of medical marijuana remain unknown. Generalizing the use of medical marijuana to all CNCP conditions does not appear to be supported by existing evidence. Clinicians should exercise caution when prescribing medical marijuana for patients, especially in those with nonneuropathic CNCP.



Differences Between African-American and European-American Women in the Association of Childhood Sexual Abuse With Initiation of Marijuana Use and Progression to Problem Use

Sartor CE^{1,2}, Agrawal A², Grant JD², Duncan AE³, Madden PA², Lynskey MT⁴, Heath AC², Bucholz KK².

1. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut
2. Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri
3. George Warren Brown School of Social Work, Washington University, St. Louis, Missouri
4. National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

<http://www.ncbi.nlm.nih.gov/pubmed/26098032>

Childhood sexual abuse (CSA) is associated with elevated risk of early marijuana use and cannabis use disorder (CUD). Both the prevalence of CSA and the course of marijuana use differ between African Americans and European Americans. The current study aimed to determine whether these differences manifest in racial/ ethnic distinctions in the association of CSA with early and problem use of marijuana.

Data were derived from female participants in a female twin study and a high-risk family study of substance use (n = 4,193, 21% African-American). Cox proportional hazard regression analyses using CSA to predict initiation of marijuana use and progression to CUD symptom(s) were conducted separately by race/ethnicity. Sibling status on the marijuana outcome was used to adjust for familial influences.

CSA was associated with both stages of marijuana use in African-American and European-American women. The association was consistent over the risk period in European-American women. In African-American women CSA predicted onset only at age 21 and older.

The association of CSA with initiation of marijuana use and progression to problem use is stable over time in European-American women, but in African-American women, it varies by developmental period. Findings suggest the importance of considering race/ethnicity in prevention efforts with this high-risk population.

Handbook Of Experimental Pharmacology • July 2015

Cannabis and Endocannabinoid Signaling in Epilepsy

By I. Katona

<http://www.ncbi.nlm.nih.gov/pubmed/26408165>

The antiepileptic potential of Cannabis sativa preparations has been historically recognized. Recent changes in legal restrictions and new well-documented cases reporting remarkably strong beneficial effects have triggered an upsurge in exploiting medical marijuana in patients with refractory epilepsy. Parallel research efforts in the last decade have uncovered the fundamental role of the endogenous cannabinoid system in controlling neuronal network excitability raising hopes for cannabinoid-based therapeutic approaches. However, emerging data show that patient responsiveness varies substantially, and that cannabis administration may sometimes even exacerbate seizures.

Hormonal status and age differentially affect tolerance to the disruptive effects of delta-9-tetrahydrocannabinol ($\Delta(9)$ -THC) on learning in female rats

Winsauer PJ1, Filipeanu CM2, Weed PF3, Sutton JL3.

1. Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center New Orleans New Orleans, LA, USA
Alcohol and Drug Abuse Center of Excellence, Louisiana State University Health Sciences Center New Orleans New Orleans, LA, USA
2. Department of Pharmacology, Howard University College of Medicine Washington, DC, USA
3. Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center New Orleans New Orleans, LA, USA

Full text with 90 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4488627/>

The effects of hormone status and age on the development of tolerance to $\Delta(9)$ -THC were assessed in sham-operated (intact) or ovariectomized (OVX) female rats that received either intraperitoneal saline or 5.6 mg/kg of $\Delta(9)$ -THC daily from postnatal day (PD) 75-180 (early adulthood onward) or PD 35-140 (adolescence onward). During this time, the four groups for each age (i.e., intact/saline, intact/THC, OVX/saline, and OVX/THC) were trained in a learning and performance procedure and dose-effect curves were established for $\Delta(9)$ -THC (0.56-56 mg/kg) and the cannabinoid type-1 receptor (CB1R) antagonist rimonabant (0.32-10 mg/kg). Despite the persistence of small rate-decreasing and error-increasing effects in intact and OVX females from both ages during chronic $\Delta(9)$ -THC, all of the $\Delta(9)$ -THC groups developed tolerance. However, the magnitude of tolerance, as well as the effect of hormone status, varied with the age at which chronic $\Delta(9)$ -THC was initiated. There was no evidence of dependence in any of the groups. Hippocampal protein expression of CB1R, AHA1 (a co-chaperone of CB1R) and HSP90 β (a molecular chaperone modulated by AHA-1) was affected more by OVX than chronic $\Delta(9)$ -THC; striatal protein expression was not consistently affected by either manipulation. Hippocampal brain-derived neurotrophic factor expression varied with age, hormone status, and chronic treatment. Thus, hormonal status differentially affects the development of tolerance to the disruptive effects of delta-9-tetrahydrocannabinol ($\Delta(9)$ -THC) on learning and performance behavior in adolescent, but not adult, female rats. These factors and their interactions also differentially affect cannabinoid signaling proteins in the hippocampus and striatum, and ultimately, neural plasticity.

Medical uses of marijuana (*Cannabis sativa*): fact or fallacy?

By W.J. Maule

<http://www.ncbi.nlm.nih.gov/pubmed/26126326>

Marijuana (*Cannabis sativa*) has been used throughout the world medically, recreationally and spiritually for thousands of years. In South Africa, from the mid-19th century to the 1920s, practitioners prescribed it for a multitude of conditions. In 1928 it was classified as a Schedule I substance, illegal, and without medical value. Ironically, with this prohibition, cannabis became the most widely used illicit recreational drug, not only in South Africa, but worldwide. Cannabis is generally regarded as enjoyable and relaxing without the addictive risks of opioids or stimulants. In alternative medicine circles it has never lost its appeal. To date 23 States in the USA have legalised its medical use despite the federal ban. Unfortunately, little about cannabis is not without controversy. Its main active ingredient, δ -9-tetrahydrocannabinol (THC), was not isolated until 1964, and it was not until the 1990s that the far-reaching modulatory activities of the endocannabinoid system in the human body was studied. This system's elucidation raises the possibility of many promising pharmaceutical applications, even as restrictions show no sign of abating. Recreational use of cannabis continues to increase, despite growing evidence of its addictive potential, particularly in the young. Public approval drives medical cannabis legalisation efforts without the scientific data normally required to justify a new medication's introduction. This review explores these controversies and whether cannabis is a panacea, a scourge, or both.

Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-2011

Joseph Schuermeyer,¹ Stacy Salomonsen-Sautel,¹ Rumi Kato Price,² Sundari Balan,² Christian Thurstone,^{1,3} Sung-Joon Min,⁴ and Joseph T. Sakai¹

¹ Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, Colorado

² Department of Psychiatry, Washington University School of Medicine, St. Louis, MO

³ Denver Health and Hospital Authority, Denver, Colorado

⁴ Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Full text with 45 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161452/>

In 2009, policy changes were accompanied by a rapid increase in the number of medical marijuana cardholders in Colorado. Little published epidemiological work has tracked changes in the state around this time. Using the National Survey on Drug Use and Health, we tested for temporal changes in marijuana attitudes and marijuana-use-related outcomes in Colorado (2003-2011) and differences within-year between Colorado and thirty-four non-medical-marijuana states (NMMS). Using regression analyses, we further tested whether patterns seen in Colorado prior to (2006-8) and during (2009-11) marijuana commercialization differed from patterns in NMMS while controlling for demographics.

Within Colorado those reporting “great-risk” to using marijuana 1-2 times/week dropped significantly in all age groups studied between 2007-8 and 2010-11 (e.g. from 45% to 31% among those 26 years and older; $p=0.0006$). By 2010-11 past-year marijuana abuse/dependence had become more prevalent in Colorado for 12-17 year olds (5% in Colorado, 3% in NMMS; $p=0.03$) and 18-25 year olds (9% vs. 5%; $p=0.02$). Regressions demonstrated significantly greater reductions in perceived risk (12-17 year olds, $p=0.005$; those 26 years and older, $p=0.01$), and trend for difference in changes in availability among those 26 years and older and marijuana abuse/dependence among 12-17 year olds in Colorado compared to NMMS in more recent years (2009-11 vs. 2006-8).

Our results show that commercialization of marijuana in Colorado has been associated with lower risk perception. Evidence is suggestive for marijuana abuse/dependence. Analyses including subsequent years 2012+ once available, will help determine whether such changes represent momentary vs. sustained effects.

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review

By K.P. Hill

<http://www.ncbi.nlm.nih.gov/pubmed/26103031>

Substance Abuse Consultation Service, McLean Hospital, Belmont, Massachusetts²Harvard Medical School, Boston, Massachusetts, USA

As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration-approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been

By E.P. Baron

Department of Neurology, Headache Center, Cleveland Clinic Neurological Institute, Cleveland, OH, USA

<http://www.ncbi.nlm.nih.gov/pubmed/26015168>

The use of cannabis, or marijuana, for medicinal purposes is deeply rooted through history, dating back to ancient times. It once held a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases, particularly headache and migraine. Through the decades, this plant has taken a fascinating journey from a legal and frequently prescribed status to illegal, driven by political and social factors rather than by science. However, with an abundance of growing support for its multitude of medicinal uses, the misguided stigma of cannabis is fading, and there has been a dramatic push for legalizing medicinal cannabis and research. Almost half of the United States has now legalized medicinal cannabis, several states have legalized recreational use, and others have legalized cannabidiol-only use, which is one of many therapeutic cannabinoids extracted from cannabis. Physicians need to be educated on the history, pharmacology, clinical indications, and proper clinical use of cannabis, as patients will inevitably inquire about it for many diseases, including chronic pain and headache disorders for which there is some intriguing supportive evidence.

The literature suggests that the medicinal use of cannabis may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. Supporting literature suggests a role for medicinal cannabis and cannabinoids in several types of headache disorders including migraine and cluster headache, although it is primarily limited to case based, anecdotal, or laboratory-based scientific research. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action, and opiate pathways, suggesting potential synergistic or similar benefits. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation.

Reviews In Medicine Suisse • June 2015

Clinical pharmacology of medical cannabinoids in chronic pain

Ing Lorenzini K, Broers B, Lalive PH, Dayer P, Desmeules J, Piguet V.

<http://www.ncbi.nlm.nih.gov/pubmed/26267945>

In Switzerland, medical cannabinoids can be prescribed under compassionate use after special authorization in justified indications such as refractory pain. Evidence of efficacy in pain is limited and the clinical benefit seems to be modest. Their drug-drug interactions (DDI) profile is poorly documented. Cytochromes P450 (CYP) 2C9 and 3A4 are involved in the metabolism of tetrahydrocannabinol and cannabidiol, which implies possible DDI with CYP450 inhibitor and inducer, such as anticonvulsivants and HIV protease inhibitors, which may be prescribed in patients with neuropathic pain.

Clinical Pharmacology And Therapeutics • June 2015

**Delta(9) -tetrahydrocannabinol and cannabidiol as potential curative agents for cancer:
A critical examination of the preclinical literature**

By C. J. Fowler

Department of Pharmacology and Clinical Neuroscience, Umeå University, Umeå, Sweden

<http://www.ncbi.nlm.nih.gov/pubmed/25669486>

An Internet search with search words “cannabis cures cancer” produce a wealth of sites claiming that cannabis has this effect. These sites are freely accessible to the general public and thus contribute to public opinion. But do delta(9) -tetrahydrocannabinol ($\Delta(9)$ -THC) and cannabidiol (CBD) cure cancer? In the absence of clinical data other than a safety study and case reports, preclinical data should be evaluated in terms of its predictive value. Using a strict approach where only concentrations and/or models relevant to the clinical situation are considered, the current preclinical data do not yet provide robust evidence that systemically administered $\Delta(9)$ -THC will be useful for the curative treatment of cancer. There is more support for an intratumoral route of administration of higher doses of $\Delta(9)$ -THC. CBD produces effects in relevant concentrations and models, although more data are needed concerning its use in conjunction with other treatment strategies.

Clinical Pharmacology And Therapeutics • June 2015

Cannabis in cancer care

Abrams D1, Guzman M2.

1. Hematology-Oncology, San Francisco General Hospital, Department of Medicine, University of California San Francisco, San Francisco, California, USA

2. Biochemistry and Molecular Biology, School of Biology, Complutense University, and Centro de Investigacion Biomedica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

<http://www.ncbi.nlm.nih.gov/pubmed/25777363>

Cannabis has been used in medicine for thousands of years prior to achieving its current illicit substance status. Cannabinoids, the active components of *Cannabis sativa*, mimic the effects of the endogenous cannabinoids (endocannabinoids), activating specific cannabinoid receptors, particularly CB1 found predominantly in the central nervous system and CB2 found predominantly in cells involved with immune function. Delta-9-tetrahydrocannabinol, the main bioactive cannabinoid in the plant, has been available as a prescription medication approved for treatment of cancer chemotherapy-induced nausea and vomiting and anorexia associated with the AIDS wasting syndrome. Cannabinoids may be of benefit in the treatment of cancer-related pain, possibly synergistic with opioid analgesics. Cannabinoids have been shown to be of benefit in the treatment of HIV-related peripheral neuropathy, suggesting that they may be worthy of study in patients with other neuropathic symptoms. Cannabinoids have a favorable drug safety profile, but their medical use is predominantly limited by their psychoactive effects and their limited bioavailability.

The Antitumor Activity of Plant-Derived Non-Psychoactive Cannabinoids

McAllister SD1, Soroceanu L, Desprez PY.

California Pacific Medical Center Research Institute, 475 Brannan Street, Suite 220, San Francisco, CA, 94107, USA
mcallis@cpmcri.org

Full text with 103 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470774/>

Through the activation primarily of CB1 receptors in the central nervous system, THC can reduce nausea, emesis and pain in cancer patients undergoing chemotherapy. During the last decade, however, several studies have now shown that CB1 and CB2 receptor agonists can act as direct antitumor agents in a variety of aggressive cancers.

In addition to THC, there are many other cannabinoids found in CS, and a majority produces little to no psychoactivity due to the inability to activate cannabinoid receptors. For example, the second most abundant cannabinoid in CS is the non-psychoactive cannabidiol (CBD). Using animal models, CBD has been shown to inhibit the progression of many types of cancer including glioblastoma (GBM), breast, lung, prostate and colon cancer.

This review will center on mechanisms by which CBD, and other plant-derived cannabinoids inefficient at activating cannabinoid receptors, inhibit tumor cell viability, invasion, metastasis, angiogenesis, and the stem-like potential of cancer cells. We will also discuss the ability of non-psychoactive cannabinoids to induce autophagy and apoptotic-mediated cancer cell death, and enhance the activity of first-line agents commonly used in cancer treatment.

Longitudinal effects of school drug policies on student marijuana use in Washington State and Victoria, Australia

Evans-Whipp TJ1, Plenty SM, Catalano RF, Herrenkohl TI, Toumbourou JW.

Full text with 60 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4386529/>

Tracy J. Evans-Whipp, Stephanie M. Plenty, and John W. Toumbourou are with the Centre for Adolescent Health, Murdoch Children's Research Institute, Parkville, Victoria, Australia. Tracy J. Evans-Whipp and Stephanie M. Plenty are also with the University of Melbourne Department of Paediatrics, Royal Children's Hospital, Parkville. John W. Toumbourou is also with the Centre for Mental Health and Wellbeing Research and School of Psychology, Deakin University, Geelong, Victoria. Richard F. Catalano and Todd I. Herrenkohl are with the Social Development Research Group, School of Social Work, University of Washington, Seattle

We examined the longitudinal effect of schools' drug policies on student marijuana use.

We used data from the International Youth Development Study, which surveyed state-representative samples of students from Victoria, Australia, and Washington State. In wave 1 (2002), students in grades 7 and 9 (n = 3264) and a school administrator from each participating school (n = 188) reported on school drug policies. In wave 2 (2003), students reported on their marijuana use. We assessed associations between student-reported and administrator-reported policy and student self-reported marijuana use 1 year later.

Likelihood of student marijuana use was higher in schools in which administrators reported using out-of-school suspension and students reported low policy enforcement. Student marijuana use was less likely where students reported receiving abstinence messages at school and students violating school policy were counseled about the dangers of marijuana use.

Schools may reduce student marijuana use by delivering abstinence messages, enforcing nonuse policies, and adopting a remedial approach to policy violations rather than use of suspensions.

Phytocannabinoids for Cancer Therapeutics: Recent Updates and Future Prospects

Patil KR, Goyal SN, Sharma C, Patil CR, Ojha S1.

Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences United Arab Emirates University, Al Ain, United Arab Emirates, UAE
shreeshojha@uaeu.ac.ae

<http://www.ncbi.nlm.nih.gov/pubmed/26179998>

Phytocannabinoids (pCBs) are lipid-soluble phytochemicals present in the plant, *Cannabis sativa* L. and non-cannabis plants which have a long history in recreation and traditional medicine. The plant and the constituents isolated were central in the discovery of the endocannabinoid system (ECS), the most new target for drug discovery. The ECS includes two G-protein-coupled receptors; the cannabinoid receptors-1 and -2 (CB1 and CB2) for marijuana's psychoactive principle $\Delta(9)$ -tetrahydrocannabinol ($\Delta(9)$ -THC), their endogenous small lipid ligands; namely anandamide (AEA) and 2-arachidonoylglycerol (2-AG), also known as endocannabinoids and the enzymes for endocannabinoid biosynthesis and degradation such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). The ECS has been suggested as a pro-homeostatic and pleiotropic signaling system activated in a time- and tissue-specific way during pathological conditions including cancer. Targeting the CB1 receptors becomes a concern because of adverse psychotropic reactions. Hence, targeting the CB2 receptors or the endocannabinoid metabolizing enzymes by pCBs obtained from plants lacking psychotropic adverse reactions has garnered interest in drug discovery. These pCBs derived from plants appear safe and effective with a wider access and availability. In the recent years, several pCBs derived other than non-cannabinoid plants have been reported to bind to and functionally interact with cannabinoid receptors and appear promising candidate for drug development including cancer therapeutics. Several of them also targets the endocannabinoid metabolizing enzymes that control endocannabinoid levels. In this article, we summarize and critically discuss the updates and future prospects of the pCBs as novel and promising candidates for cancer therapeutics.

Pediatric Neurology • May 2015

Pure cannabidiol in the treatment of malignant migrating partial seizures in infancy: a case report

Saade D1, Joshi C2.

1,2. Division of Pediatric Neurology, University of Iowa Children's Hospital, Iowa City, Iowa
Electronic address: dimah-saade@uiowa.edu

<http://www.ncbi.nlm.nih.gov/pubmed/25882081>

Malignant migrating partial seizures in infancy is a devastating pharmacoresistent epileptic encephalopathy of unknown etiology characterized by onset in the first 6 months of life, continuous migrating focal seizures with corresponding multifocal electroencephalographic discharges, developmental deterioration, and early mortality. Recent widespread interest in the nonpsychoactive component of the cannabis plant, cannabidiol, as a potential treatment for refractory devastating epilepsies has led to individual trials initiated by families or physicians in states that have legalized medical marijuana with anecdotal success.

We describe a now 10-month-old boy with malignant migrating partial seizures in infancy who made developmental gains and demonstrated sustained seizure reduction with the addition of cannabidiol to his antiepileptic regimen.

This report supports a role for cannabidiol in the treatment of malignant migrating partial seizures in infancy.

The Use of Medicinal Marijuana for Posttraumatic Stress Disorder: A Review of the Current Literature

Stephanie Yarnell, MD, PhD
Department of Psychiatry, Yale University, New Haven, Connecticut, USA
Email: Stephanie.yarnell@yale.edu

Full text with 46 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4578915/>

Medicinal marijuana has already been legalized in over 23 states with more considering legalization. Despite the trend toward legalization, to date, there has been no systematic review of the existing literature for the efficacy of medicinal marijuana for many of the conditions for which it is proposed to treat. This study seeks to understand the current literature regarding the use of medicinal marijuana in the treatment of posttraumatic stress disorder (PTSD).

PubMed and PsycINFO databases were searched until April 2014 for articles outlining outcomes of case files, control studies, and observational studies regarding the efficacy of medicinal marijuana in treating PTSD. Various combinations of the following search terms were used: marijuana, medicinal marijuana, cannabis, cannabinoid, PTSD, efficacy, trial, and neurobiology. Full text of each article was reviewed, and those directly addressing the question of efficacy of medicinal marijuana on PTSD symptomatology were included. Data were extracted from a total of 46 articles. Analysis revealed that most reports are correlational and observational in basis with a notable lack of randomized, controlled studies. Many of the published studies suggest a decrease in PTSD symptoms with marijuana use. Though the directionality of cannabis use and PTSD could not be fully differentiated at this time, there appears to also be a correlation between PTSD and problematic cannabis use. Despite this finding, there is a growing amount of neurobiological evidence and animal studies suggesting potential neurologically based reasons for the reported efficacy.

Posttraumatic stress disorder is 1 of the approved conditions for medicinal marijuana in some states. While the literature to date is suggestive of a potential decrease in PTSD symptomatology with the use of medicinal marijuana, there is a notable lack of large-scale trials, making any final conclusions difficult to confirm at this time.

Weeding out bad waves: towards selective cannabinoid circuit control in epilepsy

Soltesz I1, Alger BE2, Kano M3, Lee SH1, Lovinger DM4, Ohno-Shosaku T5, Watanabe M6.

1. Department of Anatomy and Neurobiology, University of California, Irvine, California 92697, USA

2. Department of Physiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA

3. Department of Neurophysiology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan

4. Section on Synaptic Pharmacology, Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, US National Institutes of Health, Bethesda, Maryland 20892, USA

5. Department of Impairment Study, Graduate School of Medical Science, Kanazawa University, Kanazawa 920-0942, Japan

6. Department of Anatomy, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, Japan

<http://www.ncbi.nlm.nih.gov/pubmed/25891509>

Endocannabinoids are lipid-derived messengers, and both their synthesis and breakdown are under tight spatiotemporal regulation. As retrograde signalling molecules, endocannabinoids are synthesized postsynaptically but activate presynaptic cannabinoid receptor 1 (CB1) receptors to inhibit neurotransmitter release. In turn, CB1-expressing inhibitory and excitatory synapses act as strategically placed control points for activity-dependent regulation of dynamically changing normal and pathological oscillatory network activity. Here, we highlight emerging principles of cannabinoid circuit control and plasticity, and discuss their relevance for epilepsy and related comorbidities. New insights into cannabinoid signalling may facilitate the translation of the recent interest in cannabis-related substances as antiseizure medications to evidence-based treatment strategies.

The relationship between cannabidiol and psychosis: A review

Silva TB1, Balbino CQ, Weiber AF.

1. Department of Health, State University of Southwestern Bahia, Jequié, Bahia, Brazil
E-Mail: thaybgs@hotmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/25954940>

Cannabis sativa is the most widely used illicit drug in the world. There is concern about its harmful effects, especially because of increasing potency, which has been reported globally. These effects seem to result from the relationship among its components, notably delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which have opposite effects. THC is considered responsible for the main psychotropic effects of the drug, while CBD seems to antagonize these effects, particularly those that induce psychosis.

We performed a PubMed literature review of research discussing the association of cannabidiol and psychosis published from 2006 to July 2014.

The effects of Cannabis seem to depend on several variables related to the type of plant, its strength, usage patterns, and intersubjective variations. CBD could be used to treat several conditions, including psychosis, when the current treatment is associated with significant side effects.

Because of the complexity of the subject, including limitations and contradictions in studies available to date, further research involving the possible antipsychotic effect and other potential positive effects of Cannabis are needed. There also are noteworthy differences between the research design parameters and recreational use of Cannabis.

The impact of marijuana decriminalization on California drivers

Pollini RA¹, Romano E², Johnson MB³, Lacey JH⁴.

^{1,2,3,4}. Pacific Institute for Research and Evaluation, 11720 Beltsville Drive, Suite 900, Beltsville, MD 20705, USA

<http://www.ncbi.nlm.nih.gov/pubmed/25765482>

The liberalization of marijuana laws has led to concerns that such changes will increase “drugged driving” and crash-related mortality. California decriminalized marijuana effective January 1, 2011; we examine the impact of this change on marijuana-involved driving.

We used laboratory testing from roadside surveys and the Fatality Analysis Reporting System (FARS) to assess impacts on weekend nighttime drivers and fatally injured drivers, respectively. We calculated marijuana prevalence (measured by laboratory-confirmed delta-9-tetrahydrocannabinol [THC] in roadside surveys and cannabinoids in FARS) and compared corresponding 95% confidence intervals (CI) to identify statistically significant changes post-decriminalization. We also conducted multiple logistic regression analyses to determine whether the odds of marijuana-involved driving increased significantly after controlling for potential confounders.

There was no statistically significant change in the prevalence of THC-positive driving among weekend nighttime drivers (n=894) in 2012 (9.2%; 95% CI: 6.3, 12.2) compared to 2010 (11.3%; 95% CI: 8.5, 14.0) or in the adjusted odds of testing positive for THC (adjusted odds ratio [AOR]=0.96; 95% CI: 0.57, 1.60). In contrast, we found a statistically significant increase in the prevalence of cannabinoids among fatally injured drivers in 2012 (17.8%; 95% CI: 14.6, 20.9) compared to the pre-decriminalization period 2008-2010 (11.8%; 95% CI: 10.3, 13.3). The adjusted odds of testing positive for cannabinoids were also significantly higher in 2012 (AOR=1.67; 95% CI: 1.28, 2.18).

Our study generated discrepant findings regarding the impact of decriminalization on marijuana-involved driving in California. Factors that may have contributed to these findings, particularly methodological factors, are discussed.

The effect of phytocannabinoids on airway hyper-responsiveness, airway inflammation, and cough

Makwana R1, Venkatasamy R2, Spina D2, Page C2.

1,2. Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science, King's College London, Waterloo, London, UK
raj.makwana@outlook.com

Full text, PDF, with 72 references

<http://jpet.aspetjournals.org/content/353/1/169.full.pdf>

Cannabis has been demonstrated to have bronchodilator, anti-inflammatory, and antitussive activity in the airways, but information on the active cannabinoids, their receptors, and the mechanisms for these effects is limited. We compared the effects of $\Delta(9)$ -tetrahydrocannabinol, cannabidiol, cannabigerol, cannabichromene, cannabidiolic acid, and tetrahydrocannabivarin on contractions of the guinea pig-isolated trachea and bronchoconstriction induced by nerve stimulation or methacholine in anesthetized guinea pigs following exposure to saline or the proinflammatory cytokine, tumor necrosis factor α (TNF- α).

Tetrahydrocannabivarin partially inhibited the TNF- α -enhanced nerve-evoked contractions, whereas the other cannabinoids were without effect. The effect of cannabidiol and $\Delta(9)$ -tetrahydrocannabinol together did not differ from that of the latter alone. Only $\Delta(9)$ -tetrahydrocannabinol inhibited TNF- α -enhanced vagal-induced bronchoconstriction, neutrophil recruitment to the airways, and citric acid-induced cough responses. TNF- α potentiated contractions of airway smooth muscle in response to nerve stimulation by enhancing postganglionic acetylcholine release. $\Delta(9)$ -Tetrahydrocannabinol and CP55940 inhibited the TNF- α -enhanced acetylcholine release, and hence contraction and bronchoconstriction, through activation of presynaptic CB(1) and CB(2) receptors. The other cannabinoids did not influence cholinergic transmission, and only $\Delta(9)$ -THC demonstrated effects on airway hyper-responsiveness, anti-inflammatory activity, and antitussive activity in the airways.

Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders

Belendiuk KA¹, Baldini LL², Bonn-Miller MO^{3,4,5}.

1. Institute of Human Development, University of California, 1121 Tolman Hall #1690, Berkeley, CA, 94720, USA

2. Palo Alto University, 1791 Arastradero Road, Palo Alto, CA, 94304, USA

3. Center of Excellence in Substance Abuse Treatment and Education, Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA, 19104, USA

4. Center for Innovation to Implementation and National Center for PTSD, VA Palo Alto Health Care System, 795 Willow Road (152-MPD), Menlo Park, CA, 94025, USA

5. Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, 3440 Market Street, Philadelphia, PA, 19104, USA

Marcel.Bonn-Miller@va.gov

lbaldini@paloalto.edu

kab@berkeley.edu

Full text with 136 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4636852/>

The present investigation aimed to provide an objective narrative review of the existing literature pertaining to the benefits and harms of marijuana use for the treatment of the most common medical and psychological conditions for which it has been allowed at the state level.

Common medical conditions for which marijuana is allowed (i.e., those conditions shared by at least 80 percent of medical marijuana states) were identified as: Alzheimer's disease, amyotrophic lateral sclerosis, cachexia/wasting syndrome, cancer, Crohn's disease, epilepsy and seizures, glaucoma, hepatitis C virus, human immunodeficiency virus/acquired immunodeficiency syndrome, multiple sclerosis and muscle spasticity, severe and chronic pain, and severe nausea. Post-traumatic stress disorder was also included in the review, as it is the sole psychological disorder for which medical marijuana has been allowed.

Studies for this narrative review were included based on a literature search in PsycINFO, MEDLINE, and Google Scholar. Findings indicate that, for the majority of these conditions, there is insufficient evidence to support the recommendation of medical marijuana at this time. A significant amount of rigorous research is needed to definitively ascertain the potential implications of marijuana for these conditions. It is important for such work to not only examine the effects of smoked marijuana preparations, but also to compare its safety, tolerability, and efficacy in relation to existing pharmacological treatments.

**Narrative review of the safety and efficacy of marijuana
for the treatment of commonly state-approved medical and psychiatric disorders**

Belendiuk KA1, Baldini LL2, Bonn-Miller MO3,4,5.

Full text with 136 references

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Proapoptotic effect of endocannabinoids in prostate cancer cells

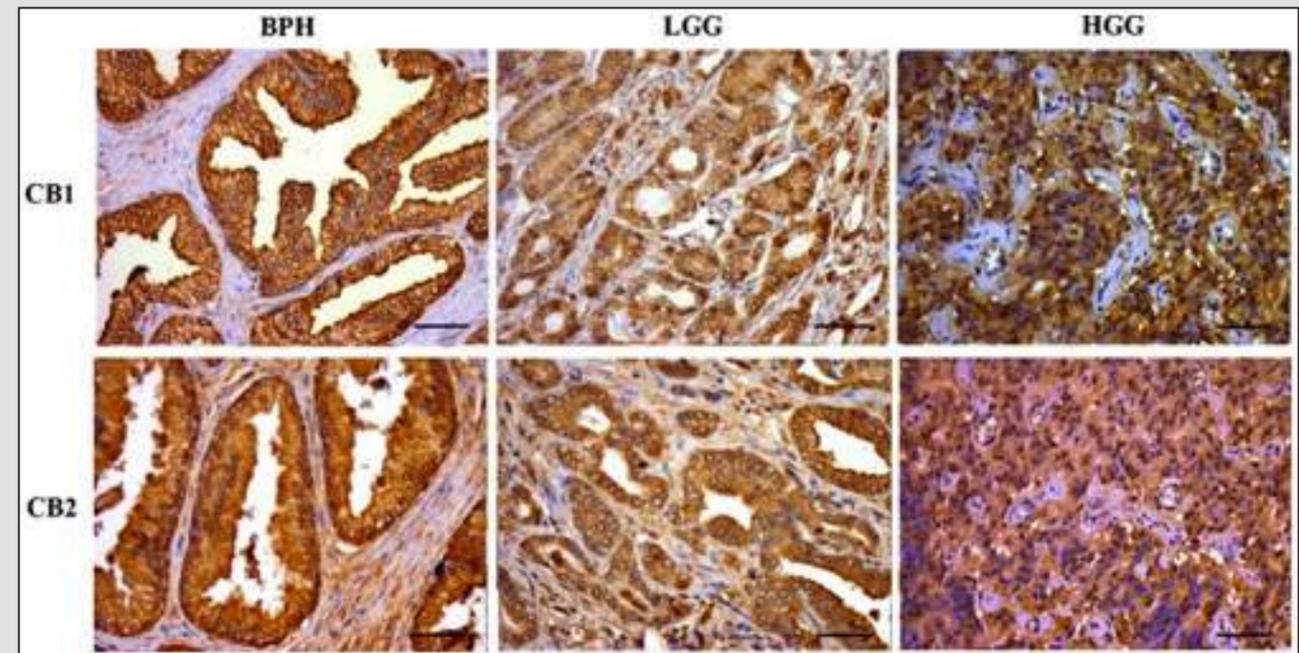
Orellana-Serradell O1, Poblete CE1, Sanchez C1, Castellón EA1, Gallegos I2, Huidobro C3, Llanos MN4, Contreras HR1.

Full text with 42 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358087/>

In the early stages, prostate cancer is androgen- dependent; therefore, medical castration has shown significant results during the initial stages of this pathology. Despite this early effect, advanced prostate cancer is resilient to such treatment. Recent evidence shows that derivatives of *Cannabis sativa* and its analogs may exert a protective effect against different types of oncologic pathologies. The purpose of the present study was to detect the presence of cannabinoid receptors (CB1 and CB2) on cancer cells with a prostatic origin and to evaluate the effect of the in vitro use of synthetic analogs. In order to do this, we used a commercial cell line and primary cultures derived from prostate cancer and benign prostatic hyperplasia. The presence of the CB1 and CB2 receptors was determined by immunohistochemistry where we showed a higher expression of these receptors in later stages of the disease (samples with a high Gleason score). Later, treatments were conducted using anandamide, 2-arachidonoyl glycerol and a

synthetic analog of anandamide, methanandamide. Using the MTT assay, we proved that the treatments produced a cell growth inhibitory effect on all the different prostate cancer cultures. This effect was demonstrated to be dose-dependent. The use of a specific CB1 receptor blocker (SR141716) confirmed that this effect was produced primarily from the activation of the CB1 receptor. In order to understand the MTT assay results, we determined cell cycle distribution by flow cytometry, which showed no variation at the different cell cycle stages in all the cultures after treatment. Treatment with endocannabinoids resulted in an increase in the percentage of apoptotic cells as determined by Annexin V assays and caused an increase in the levels of activated caspase-3 and a reduction in the levels of Bcl-2 confirming that the reduction in cell viability noted in the MTT assay was caused by the activation of the apoptotic pathway. Finally, we observed that endocannabinoid treatment activated the Erk pathway and at the same time, produced a decrease in the activation levels of the Akt pathway. Based on these results, we suggest that endocannabinoids may be a beneficial option for the treatment of prostate cancer that has become nonresponsive to common therapies.



Above, immunohistochemical staining for CB1-R and CB2-R in BPH, LGG and HGG (x40 magnification). Scale bar, 50 μ m. BPH, benign prostatic hyperplasia tissue; LGG, low Gleason grade prostatic cancer tissue; HGG, high Gleason grade prostatic cancer tissue.

Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Elmes MW1, Kaczocha M2, Berger WT3, Leung K1, Ralph BP1, Wang L1, Sweeney JM1, Miyauchi JT4, Tsirka SE4, Ojima I3, Deutsch DG5.

1. From the Departments of Biochemistry and Cell Biology
2. From the Departments of Biochemistry and Cell Biology, Anesthesiology, and
3. Chemistry, the Institute of Chemical Biology and Drug Discovery, and
4. the Department of Pharmacological Sciences, Stony Brook University, Stony Brook, New York
5. From the Departments of Biochemistry and Cell Biology, Dale
Deutsch@Stonybrook.edu

Full text with 73 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4423662/>

Δ (9)-Tetrahydrocannabinol (THC) and cannabidiol (CBD) occur naturally in marijuana (Cannabis) and may be formulated, individually or in combination in pharmaceuticals such as Marinol or Sativex. Although it is known that these hydrophobic compounds can be transported in blood by albumin or lipoproteins, the intracellular carrier has not been identified.

Recent reports suggest that CBD and THC elevate the levels of the endocannabinoid anandamide (AEA) when administered to humans, suggesting that phytocannabinoids target cellular proteins involved in endocannabinoid clearance.

Fatty acid-binding proteins (FABPs) are intracellular proteins that mediate AEA transport to its catabolic enzyme fatty acid amide hydrolase (FAAH). By computational analysis and ligand displacement assays, we show that at least three human FABPs bind THC and CBD and demonstrate that THC and CBD inhibit the cellular uptake and catabolism of AEA by targeting FABPs. Furthermore, we show that in contrast to rodent FAAH, CBD does not inhibit the enzymatic actions of human FAAH, and thus FAAH inhibition cannot account for the observed increase in circulating AEA in humans following CBD consumption. Using computational molecular docking and site-directed mutagenesis we identify key residues within the active site of FAAH that confer the species-specific sensitivity to inhibition by CBD. Competition for FABPs may in part or wholly explain the increased circulating levels of endocannabinoids reported after consumption of cannabinoids.

These data shed light on the mechanism of action of CBD in modulating the endocannabinoid tone in vivo and may explain, in part, its reported efficacy toward epilepsy and other neurological disorders.

British Journal Of Pharmacology • April 2015

$\Delta(9)$ Tetrahydrocannabinol attenuates Staphylococcal enterotoxin B-induced inflammatory lung injury and prevents mortality in mice by modulation of miR-17-92 cluster and induction of T-regulatory cells

Rao R1, Nagarkatti PS, Nagarkatti M.

1. Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, SC, USA

Full text with 71 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4376457/>

Staphylococcal enterotoxin B (SEB) is a potent activator of V β 8⁺T-cells resulting in the clonal expansion of 30% of the T-cell pool. Consequently, this leads to the release of inflammatory cytokines, toxic shock, and eventually death. In the current study, we investigated if $\Delta(9)$ tetrahydrocannabinol (THC), a cannabinoid known for its anti-inflammatory properties, could prevent SEB-induced mortality and alleviate symptoms of toxic shock.

We report, for the first time a role for the miRNA 17-92 cluster in SEB-mediated inflammation. Furthermore, our results suggest that THC is a potent anti-inflammatory compound that may serve as a novel therapeutic to suppress SEB-induced pulmonary inflammation by modulating critical miRNA involved in SEB-induced toxicity and death.

Epilepsy Behavior • April 2015

Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy

Press CA1, Knupp KG1, Chapman KE2.

1,2. Department of Pediatrics and Neurology, Children's Hospital Colorado, University of Colorado, Anschutz Medical Campus, CO, USA
Electronic address: kevin.chapman@childrenscolorado.org.

<http://www.ncbi.nlm.nih.gov/pubmed/25845492>

Oral cannabis extracts (OCEs) have been used in the treatment of epilepsy; however, no studies demonstrate clear efficacy. We report on a cohort of pediatric patients with epilepsy who were given OCE and followed in a single tertiary epilepsy center.

Our retrospective study of oral cannabis extracts use in pediatric patients with epilepsy demonstrates that some families reported patient improvement with treatment; however, we also found a variety of challenges and possible confounding factors in studying oral cannabis extracts retrospectively in an open-labeled fashion. We strongly support the need for controlled, blinded studies to evaluate the efficacy and safety of oral cannabis extracts for treatment of pediatric epilepsies using accurate seizure counts, formal neurocognitive assessments, as well as EEG as a biomarker.

This study provides Class III evidence that oral cannabis extract is well tolerated by children and adolescents with epilepsy.

Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome

Hussain SA1, Zhou R2, Jacobson C2, Weng J2, Cheng E2, Lay J2, Hung P2, Lerner JT2, Sankar R2.

1,2. Division of Pediatric Neurology, Mattel Children's Hospital at UCLA, David Geffen School of Medicine, Los Angeles, CA, USA
Electronic address: shussain@mednet.ucla.edu

<http://www.ncbi.nlm.nih.gov/pubmed/25935511>

There is a great need for safe and effective therapies for treatment of infantile spasms (IS) and Lennox-Gastaut syndrome (LGS). Based on anecdotal reports and limited experience in an open-label trial, cannabidiol (CBD) has received tremendous attention as a potential treatment for pediatric epilepsy, especially Dravet syndrome.

However, there is scant evidence of specific utility for treatment of IS and LGS. We sought to document the experiences of children with IS and/or LGS who have been treated with CBD-enriched cannabis preparations.

Although this study suggests a potential role for CBD in the treatment of refractory childhood epilepsy including IS and LGS, it does not represent compelling evidence of efficacy or safety. From a methodological standpoint, this study is extraordinarily vulnerable to participation bias and limited by lack of blinded outcome ascertainment. Appropriately controlled clinical trials are essential to establish efficacy and safety.

Arquivos de Neuropsiquiatria • April 2015

Cannabinoids in neurology—Brazilian Academy of Neurology

Brucki SM1, Frota NA1, Schestatsky P1, Souza AH1, Carvalho VN1, Manreza ML1, Mendes MF1, Comini-Frota E1, Vasconcelos C1, Tumas V1, Ferraz HB1, Barbosa E1, Jurno ME1.

Academia Brasileira de Neurologia, Sao Paulo, SP, Brazil

<http://www.ncbi.nlm.nih.gov/pubmed/25992535>

The use of cannabidiol in some neurological conditions was allowed by Conselho Regional de Medicina de São Paulo and by Agência Nacional de Vigilância Sanitária (ANVISA). Specialists on behalf of Academia Brasileira de Neurologia prepared a critical statement about use of cannabidiol and other cannabis derivatives in neurological diseases.

The Effects of Medical Marijuana Laws on Potency

Eric L. Sevigny, Rosalie Liccardo Pacula, and Paul Heaton

Department of Criminology and Criminal Justice, University of South Carolina, 1305 Greene St., Columbia, SC, USA
Email ude.cs.xobliam@yngives :

Full text with 77 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4010875/>

Marijuana potency has risen dramatically over the past two decades. In the United States, it is unclear whether state medical marijuana policies have contributed to this increase.

Employing a differences-in-differences model within a mediation framework, we analyzed data on $n = 39,157$ marijuana samples seized by law enforcement in 51 U.S. jurisdictions between 1990-2010, producing estimates of the direct and indirect effects of state medical marijuana laws on potency, as measured by $\Delta 9$ -tetrahydrocannabinol content.

We found evidence that potency increased by a half percentage point on average after legalization of medical marijuana, although this result was not significant. When we examined specific medical marijuana supply provisions, results suggest that legal allowances for retail dispensaries had the strongest influence, significantly increasing potency by about one percentage point on average. Our mediation analyses examining the mechanisms through which medical marijuana laws influence potency found no evidence of direct regulatory impact. Rather, the results suggest that the impact of these laws occurs predominantly through a compositional shift in the share of the market captured by high-potency sinsemilla.

Our findings have important implications for policymakers and those in the scientific community trying to understand the extent to which greater availability of higher potency marijuana increases the risk of negative public health outcomes, such as drugged driving and drug-induced psychoses. Future work should reconsider the impact of medical marijuana laws on health outcomes in light of dramatic and ongoing shifts in both marijuana potency and the medical marijuana policy environment.

Endocannabinoid degradation inhibition improves neurobehavioral function, blood-brain barrier integrity, and neuroinflammation following mild traumatic brain injury

Katz PS1, Sulzer JK, Impastato RA, Teng SX, Rogers EK, Molina PE.

Department of Physiology, Alcohol and Drug Abuse Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Full text with 64 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4348366/>

Traumatic brain injury (TBI) is an increasingly frequent and poorly understood condition lacking effective therapeutic strategies. Inflammation and oxidative stress (OS) are critical components of injury, and targeted interventions to reduce their contribution to injury should improve neurobehavioral recovery and outcomes. Recent evidence reveals potential protective, yet short-lived, effects of the endocannabinoids (ECs), 2-arachidonoyl glycerol (2-AG) and N-arachidonoyl-ethanolamine (AEA), on neuroinflammatory and OS processes after TBI. The aim of this study was to determine whether EC degradation inhibition after TBI would improve neurobehavioral recovery by reducing inflammatory and oxidative damage. Adult male Sprague-Dawley rats underwent a 5-mm left lateral craniotomy, and TBI was induced by lateral fluid percussion. TBI produced apnea (17 ± 5 sec) and a delayed righting reflex (479 ± 21 sec). Thirty minutes post-TBI, rats were randomized to receive intraperitoneal injections of vehicle (alcohol, emulphor, and saline; 1:1:18) or a selective inhibitor of 2-AG (JZL184, 16 mg/kg) or AEA (URB597, 0.3 mg/kg) degradation. At 24 h post-TBI, animals showed significant neurological and behavioral impairment as well as disruption of blood-brain barrier (BBB) integrity. Improved neurological and behavioral function was observed in JZL184-treated animals. BBB integrity was protected in both JZL184- and URB597-treated animals. No significant differences in ipsilateral cortex messenger RNA expression of interleukin (IL)-1 β , IL-6, chemokine (C-C motif) ligand 2, tumor necrosis factor alpha, cyclooxygenase 2 (COX2), or nicotinamide adenine dinucleotide phosphate oxidase (NOX2) and protein expression of COX2 or NOX2 were observed across experimental groups. Astrocyte and microglia activation was significantly increased post-TBI, and treatment with JZL184 or URB597 blocked activation of both cell types. These findings suggest that EC degradation inhibition post-TBI exerts neuroprotective effects. Whether repeated dosing would achieve greater protection remains to be examined.

Phytotherapy Research • March 2015

Therapeutic potential of cannabinoids in counteracting chemotherapy-induced adverse effects: an exploratory review

Ostadhadi S1, Rahmatollahi M, Dehpour AR, Rahimian R.

Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<http://www.ncbi.nlm.nih.gov/pubmed/25504799>

Cannabinoids (the active constituents of *Cannabis sativa*) and their derivatives have got intense attention during recent years because of their extensive pharmacological properties. Cannabinoids first developed as successful agents for alleviating chemotherapy associated nausea and vomiting. Recent investigations revealed that cannabinoids have a wide range of therapeutic effects such as appetite stimulation, inhibition of nausea and emesis, suppression of chemotherapy or radiotherapy-associated bone loss, chemotherapy-induced nephrotoxicity and cardiotoxicity, pain relief, mood amelioration, and last but not the least relief from insomnia. In this exploratory review, we scrutinize the potential of cannabinoids to counteract chemotherapy-induced side effects. Moreover, some novel and yet important pharmacological aspects of cannabinoids such as antitumoral effects will be discussed.

Journal Of Food Science Technology • March 2015

Effect of ultrasound pre-treatment of hemp (*Cannabis sativa* L.) seed on supercritical CO₂ extraction of oil

Da Porto C1, Natolino A1, Decorti D1.

Department of Food Science, University of Udine, Udine, Italy

Full text with 29 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4348290/>

Ultrasound pre-treatment of intact hemp seeds without any solvent assistance was carried out for 10, 20 and 40 min prior to SCCO₂ extraction at 40 °C, 300 bar and 45 kg CO₂/kg feed. Sonication time effect on SC-CO₂ extraction was investigated by the extraction kinetics. The maximum extraction yield was estimated to be 24.03 (% w/w) after 10 min of ultrasonic pre-treatment. The fatty acid compositions of the oils extracted by SC-CO₂ without and with ultrasound pre-treatments was analyzed using gas chromatography. It was shown that the content of linoleic, α -linolenic and oleic acids (the most abundant unsaturated fatty acids) of the hemp seed oils were not affected significantly by the application of ultrasound. UV spectroscopy indices (K232 and K268) and antiradical capacity were used to follow the quality of oils. Significant were the changes in their antiradical capacity due to ultrasound treatment. A comparison with the oil extracted by Soxhlet was also given.

Impact of marijuana use on self-rated cognition in young adult men and women

Conroy DA1, Kurth ME, Brower KJ, Strong DR, Stein MD.

1. University of Michigan Addiction Research Center, Ann Arbor, Michigan

<http://www.ncbi.nlm.nih.gov/pubmed/25864605>

Marijuana (MJ) is a widely used substance that has been shown to impair cognition in laboratory settings. There is a growing number of medical MJ dispensaries and state policies permitting the use of MJ in the United States. This study is a naturalistic study that explores the association of same day MJ use on self-rated cognition in young adult men and women.

Forty-eight (n = 48) young adults (22 F; mean age = 22.3) participated. After a baseline assessment, participants made daily phone calls to study staff over the next 3 weeks. Cumulative minutes of MJ use in the last 24-hours were assessed. Demographic information collected and self-ratings of cognitive impairment were assessed using six questions about areas of difficulty thinking each day.

There was a significant relationship between greater number of minutes of MJ use and higher levels of self-rated cognitive difficulties (b = .004; SE = .001; p < .006). There was no main effect of gender (b = 1.0; SE = .81; p < .22). Planned evaluation of the interaction between gender and minutes of MJ use was not significant statistically, suggesting a similar relationship between minutes of MJ use and cognitive difficulties among women compared to men (p < .54).

There is an association between current and heavy MJ use and self-perceived cognitive ability in both males and females. These findings reveal important information regarding one consequence of MJ use that has real-world meaning to young adult smokers.

Support Care Cancer • March 2015

Inhaled medicinal cannabis and the immunocompromised patient

Ruchlemer R1, Amit-Kohn M, Raveh D, Hanuš L.

Department of Hematology, Shaare Zedek Medical Center, 12 Shmuel Biet St., 91031, Jerusalem, Israel,
ruc@szmc.org.il

<http://www.ncbi.nlm.nih.gov/pubmed/25216851>

Medicinal cannabis is an invaluable adjunct therapy for pain relief, nausea, anorexia, and mood modification in cancer patients and is available as cookies or cakes, as sublingual drops, as a vaporized mist, or for smoking. However, as with every herb, various microorganisms are carried on its leaves and flowers which when inhaled could expose the user, in particular immunocompromised patients, to the risk of opportunistic lung infections, primarily from inhaled molds. The objective of this study was to identify the safest way of using medicinal cannabis in immunosuppressed patients by finding the optimal method of sterilization with minimal loss of activity of cannabis. We describe the results of culturing the cannabis herb, three methods of sterilization, and the measured loss of a main cannabinoid compound activity. Systematic sterilization of medicinal cannabis can eliminate the risk of fatal opportunistic infections associated with cannabis among patients at risk.

Journal Of Dietary Supplements • March 2015

**Potential oil yield, fatty acid composition, and oxidation stability
of the hempseed oil from four *Cannabis sativa* L. cultivars**

Da Porto C1, Decorti D, Natolino A.

Department of Food Science, University of Udine, Udine, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/24552275>

The cultivation of four industrial hemp cultivars (Felina 32, Chamaeleon, Uso31, and Finola) was investigated for oil production in the north-east of Italy along two years. The oils of all cultivars resulted in rich amount of linoleic acid (ω -6) and α -linolenic acid (ω -3). Felina 32 and Chamaeleon oils exhibited the highest amount of linoleic acid (59%) and α -linolenic acid (18%). Finola and Uso31 oils resulted in the richest of γ -linolenic acid (5-6%).

All hempseed oils presented high oxidation stability and an acceptable initial quality. It is suggested that these oils can be used to produce EFA dietary supplements high in ω -6 and ω -3 of vegetal origin.

CA Cancer Journal • March 2015

Medical marijuana for cancer

By J.L. Kramer

Medical Editor, American Cancer Society, Atlanta, GA

Full text, PDF, with 151 references

<http://onlinelibrary.wiley.com/doi/10.3322/caac.21260/epdf>

Marijuana has been used for centuries, and interest in its medicinal properties has been increasing in recent years. Investigations into these medicinal properties has led to the development of cannabinoid pharmaceuticals such as dronabinol, nabilone, and nabiximols. Dronabinol is best studied in the treatment of nausea secondary to cancer chemotherapy and anorexia associated with weight loss in patients with acquired immune deficiency syndrome, and is approved by the US Food and Drug Administration for those indications. Nabilone has been best studied for the treatment of nausea secondary to cancer chemotherapy. There are also limited studies of these drugs for other conditions. Nabiximols is only available in the United States through clinical trials, but is used in Canada and the United Kingdom for the treatment of spasticity secondary to multiple sclerosis and pain. Studies of marijuana have concentrated on nausea, appetite, and pain. This article will review the literature regarding the medical use of marijuana and these cannabinoid pharmaceuticals (with emphasis on indications relevant to oncology), as well as available information regarding adverse effects of marijuana use.

Prevalence of medical marijuana use in California, 2012

Ryan-Ibarra S1, Induni M, Ewing D.

Survey Research Group, Public Health Institute, Sacramento, California, USA

<http://www.ncbi.nlm.nih.gov/pubmed/25255903>

The US Drug Enforcement Agency classifies marijuana as an illegal substance, yet in 22 states marijuana is legal for medicinal use. In 1996, California legalised the use of marijuana for medicinal purposes, but population-based data describing medical marijuana users in the state has not been available. Our aim was to examine the demographic differences between users and non-users of medical marijuana in California utilising population-based data.

We used data from the California Behavioral Risk Factor Surveillance System 2012, an annual, random-digit-dial state-wide telephone survey that collects health data from a representative adult sample (n = 7525). Age-adjusted prevalence rates were estimated.

Five percent of adults in California reported ever using medical marijuana, and most users believed that medical marijuana helped alleviate symptoms or treat a serious medical condition. Prevalence was similar when compared by gender, education and region. Prevalence of ever using medical marijuana was highest among white adults and younger adults ages 18-24 years, although use was reported by every racial/ethnic and age group examined in our study and ranged from 2% to 9%.

Our study's results lend support to the idea that medical marijuana is used equally by many groups of people and is not exclusively used by any one specific group. As more states approve marijuana use for medical purposes, it is important to track medical marijuana use as a health-related behaviour and risk factor.

Relationship between cannabinoids content and composition of fatty acids in hempseed oils

Petrović M1, Debeljak Ž2, Kezić N3, Džidara P3.

1. Food Control Center, Faculty of Food Technology and Biotechnology, University of Zagreb, Jagićeva 31, 10000 Zagreb, Croatia
2. Department of Clinical Laboratory Diagnostics, Osijek Clinical Hospital, J. Huttlera 4, 31000 Osijek, Croatia
3. Food Control Center, Faculty of Food Technology and Biotechnology, University of Zagreb, Jagićeva 31, 10000 Zagreb, Croatia
Electronic address: mpetrovic@pbf.hr

<http://www.ncbi.nlm.nih.gov/pubmed/25306338>

Hempseed oils acquired on the Croatian markets were characterised by cannabinoid content and fatty acid composition. The new method for determination of cannabinoid content was developed and validated in the range of 0.05-60 mg/kg, and **the content of tetrahydrocannabinol varied between 3.23 and 69.5 mg/kg.**

Large differences among the samples were obtained for phenotype ratio suggesting that not all of analysed hempseed oils were produced from industrial hemp. Sample clustering based on cannabinoid content assigned samples to two groups closely related to the phenotype ratios obtained. The results of this study confirm that hempseed oil is a good source of polyunsaturated fatty acids, especially γ -linolenic and stearidonic acid, but the content varies a lot more than the omega-6/omega-3 ratio. The grouping of samples on fatty acid content assigned samples to two groups which were consistent with the groups obtained based on cannabinoid content clustering.

A systematic review of the antipsychotic properties of cannabidiol in humans

Iseger TA1, Bossong MG2.

1. Institute of Psychiatry, Department of Psychosis Studies, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

2. Institute of Psychiatry, Department of Psychosis Studies, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

Electronic address: m.bossong@umcutrecht.nl

<http://www.ncbi.nlm.nih.gov/pubmed/25667194>

Despite extensive study over the past decades, available treatments for schizophrenia are only modestly effective and cause serious metabolic and neurological side effects. Therefore, there is an urgent need for novel therapeutic targets for the treatment of schizophrenia. A highly promising new pharmacological target in the context of schizophrenia is the endocannabinoid system. Modulation of this system by the main psychoactive component in cannabis, $\Delta 9$ -tetrahydrocannabinol (THC), induces acute psychotic effects and cognitive impairment. However, the non-psychotropic, plant-derived cannabinoid agent cannabidiol (CBD) may have antipsychotic properties, and thus may be a promising new agent in the treatment of schizophrenia. Here we review studies that investigated the antipsychotic properties of CBD in human subjects. Results show the ability of CBD to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. In addition, CBD may lower the risk for developing psychosis that is related to cannabis use. These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. The first small-scale clinical studies with CBD treatment of patients with psychotic symptoms further confirm the potential of CBD as an effective, safe and well-tolerated antipsychotic compound, although large randomised clinical trials will be needed before this novel therapy can be introduced into clinical practice.

Researchers will score more-powerful varieties of the drug courtesy of the National Institute on Drug Abuse Marijuana gears up for high production in US labs

By Sara Reardon

<http://www.nature.com/news/marijuana-gears-up-for-production-high-in-us-labs-1.17129>

The University of Mississippi in Oxford grows marijuana for US researchers under a government contract. Residents of 23 US states can buy medical marijuana to treat everything from cancer pain to anxiety, but US scientists must wade through onerous paperwork to score the drug for study. Their sole dealer is the National Institute on Drug Abuse (NIDA), which has a contract with the University of Mississippi in Oxford to produce marijuana for research purposes.

The agency has long faced complaints that its marijuana is too weak to represent what is sold on the street, and contains low levels of the non-psychedelic chemicals that show therapeutic promise for conditions such as epilepsy and chronic pain. Now, with legal marijuana increasingly available to the US public, NIDA is quietly changing course — working to expand the amount and variety of the drug available for study.

“We want to be able to evaluate the claims that marijuana is therapeutically beneficial” and to explore treatments for addiction, says Nora Volkow, director of NIDA in Rockville, Maryland.

In 2014, the institute increased its spending on research marijuana by 50%. Annual production at the University of Mississippi farm, where all the agency supplies are grown, soared from 18 to 600 kilograms, and the crop harvested late last year includes two new strains. One has low concentrations of tetrahydrocannabinol (THC), marijuana’s

primary active ingredient, but high levels of cannabidiol, a non-hallucinogenic substance that seems to have therapeutic effects. The second has relatively balanced levels of the two chemicals.

Mahmoud ElSohly, who directs the University of Mississippi cultivation programme, says that the new strains will soon be ready to ship to researchers. But the farm’s improved offerings may not appease NIDA’s critics — including US states such as Colorado, which legalized recreational pot use in 2012. In December, the Colorado state government asked the federal government to allow state universities to grow marijuana for research, citing bureaucratic hurdles in obtaining products from NIDA and from private growers overseas.

And the agency’s most potent strains still fall short of the most powerful street pot. At least 90% of the marijuana seized by the US Drug Enforcement Administration (DEA) contains high levels of THC — often more than 20% by weight. NIDA’s pot contains 12% THC at most. “Let me just say: lame,” says Rick Doblin, director of the Multidisciplinary Association for Psychedelic Studies, a non-profit organization in Santa Cruz, California, that funds research into mind-altering drugs.

It is not clear how NIDA’s plants compare with those distributed by medical-marijuana dispensaries. Although legal under local state laws, such dispensaries are still illegal under federal law, so research-

ers cannot simply buy pot there to test. And because Congress voted last year to prohibit the federal government from raiding such facilities, the products are not available for NIDA to study, either. "I don't know what dispensaries have," says ElSohly. "I wish I did."

The pool of US scientists who study marijuana is small, and to Volkow's surprise, it has not grown despite the increasing availability of legal pot and NIDA's efforts to ease limits on such research. Volkow suspects that scientists may simply need time to plan new experiments that involve marijuana, which must be evaluated by NIDA, the DEA and, in the case of clinical research, the Food and Drug Administration.

Donald Abrams, a physician at the University of California, San Francisco, who studies cannabinoids as cancer therapies, offers another theory. The rise of precision medical technologies such as gene therapy makes it less attractive to study a plant, he says — particularly one as controversial as marijuana.

Doblin suggests that successful therapies derived from marijuana are most likely to emerge outside the United States, in countries where licensed growers can provide the plant at relatively low cost and in high quantities. GW Pharmaceuticals in Salisbury, UK, uses marijuana from its private farm to produce Sativex (nabiximols), a multiple-sclerosis drug that is approved for use in 27 countries. And private growers in Israel and Canada produce research- and clinical-grade



The University of Mississippi in Oxford, above, where marijuana is carefully grown for US researchers under government contract

pot that is cheaper than NIDA's crop. The agency charges researchers US\$1,525 per kilogram, or \$7 per cigarette.

NIDA says that it plans to limit its pot programme to individual researchers for the time being. But there is a nascent push in Congress to end the agency's monopoly on research marijuana: bipartisan legislation introduced in the Senate would allow at least three growers to obtain licences to cultivate pot for studies.

If the US government decides to expand legal marijuana production significantly, Canada could serve as a model. In April 2014, the Canadian government began allowing private firms to apply to grow medical marijuana; it has since awarded 16 licences. Canadian researchers who want to study marijuana or perform clinical trials

obtain the drug by partnering with a grower. Because multiple companies hold licences, there is wide diversity in the strains available.

"The system that's implemented right now will allow for really good collaborations," says Joshua Eades, chief science officer of the medical-marijuana producer Tilray in Nanaimo, Canada. The company is working with researchers at the University of British Columbia Okanagan in Kelowna on an 40-person clinical trial of marijuana to treat post-traumatic stress disorder. Expected to start in early summer, it will be one of the largest-ever tests of marijuana for mental health. With pot increasingly available to science outside the United States, Doblin says, "the NIDA monopoly is doomed."

Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users

Hindocha C1, Freeman TP2, Schafer G2, Gardener C2, Das RK2, Morgan CJ3, Curran HV2.

1,2. Clinical Psychopharmacology Unit, University College London, UK

3. Clinical Psychopharmacology Unit, University College London, UK

Department of Psychology, University of Exeter, UK

Electronic address: c.hindocha@ucl.ac.uk

Full text with 52 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4398332/>

Acute administration of the primary psychoactive constituent of cannabis, Δ -9-tetrahydrocannabinol (THC), impairs human facial affect recognition, implicating the endocannabinoid system in emotional processing. Another main constituent of cannabis, cannabidiol (CBD), has seemingly opposite functional effects on the brain. This study aimed to determine the effects of THC and CBD, both alone and in combination on emotional facial affect recognition. 48 volunteers, selected for high and low frequency of cannabis use and schizotypy, were administered, THC (8mg), CBD (16mg), THC+CBD (8mg+16mg) and placebo, by inhalation, in a 4-way, double-blind, placebo-controlled crossover design. They completed an emotional facial affect recognition task including fearful, angry, happy, sad, surprise and disgust faces varying in intensity from 20% to 100%. A visual analogue scale (VAS) of feeling 'stoned' was also completed. In comparison to placebo, CBD improved emotional facial affect recognition at 60% emotional intensity; THC was detrimental to the recognition of ambiguous faces of 40% intensity. The combination of THC+CBD produced no impairment. Relative to placebo, both THC alone and combined THC+CBD equally increased feelings of being 'stoned'. CBD did not influence feelings of 'stoned'. No effects of frequency of use or schizotypy were found. In conclusion, CBD improves recognition of emotional facial affect and attenuates the impairment induced by THC. This is the first human study examining the effects of different cannabinoids on emotional processing. It provides preliminary evidence that different pharmacological agents acting upon the endocannabinoid system can both improve and impair recognition of emotional faces.

A systematic review of the antipsychotic properties of cannabidiol in humans

Iseger TA1, Bossong MG2.

1. Institute of Psychiatry, Department of Psychosis Studies, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

2. Institute of Psychiatry, Department of Psychosis Studies, King's College London, 16 De Crespigny Park, London SE5 8AF, UK

Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

Electronic address: m.bossong@umcutrecht.nl

<http://www.ncbi.nlm.nih.gov/pubmed/25667194>

Despite extensive study over the past decades, available treatments for schizophrenia are only modestly effective and cause serious metabolic and neurological side effects. Therefore, there is an urgent need for novel therapeutic targets for the treatment of schizophrenia. A highly promising new pharmacological target in the context of schizophrenia is the endocannabinoid system. Modulation of this system by the main psychoactive component in cannabis, Δ^9 -tetrahydrocannabinol (THC), induces acute psychotic effects and cognitive impairment. However, the non-psychotropic, plant-derived cannabinoid agent cannabidiol (CBD) may have antipsychotic properties, and thus may be a promising new agent in the treatment of schizophrenia. Here we review studies that investigated the antipsychotic properties of CBD in human subjects. Results show the ability of CBD to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. In addition, CBD may lower the risk for developing psychosis that is related to cannabis use. These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. The first small-scale clinical studies with CBD treatment of patients with psychotic symptoms further confirm the potential of CBD as an effective, safe and well-tolerated antipsychotic compound, although large randomised clinical trials will be needed before this novel therapy can be introduced into clinical practice.

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**Words Can Be Deceiving:
A Review of Variation Among Legally Effective Medical Marijuana Laws in the United States**

Rosalie Liccardo Pacula, Ph.D., Priscillia Hunt, Ph.D., and Anne Boustead, J.D.
RAND Corporation

Full text with 6 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4314612/>

When voters in two US states approved the recreational use of marijuana in 2012, public debates for how best to promote and protect public health and safety started drawing implications from states' medical marijuana laws. However, many of the discussions were simplified to the notion that states either have a medical marijuana law or do not; little reference was made to the fact that legal provisions differ across states. This study seeks to clarify the characteristics of medical marijuana laws in place since 1990 that are most relevant to consumers/patients and categorizes those aspects most likely to affect the prevalence of use, and consequently the intensity of public health and welfare effects. Evidence shows treating medical marijuana laws as homogeneous across states is misleading and does not reflect the reality of medical marijuana lawmaking. This variation likely has implications for use and health outcomes, and thus states' public health.

Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium

Zhang LR1, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, Woll PJ, Orlov I, Cox B.
Cannabis and Respiratory Disease Research Group of New Zealand

Brhane Y, Liu G, Hung RJ.
Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada

Full text with 45 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4262725/>

To investigate the association between cannabis smoking and lung cancer risk, data on 2,159 lung cancer cases and 2,985 controls were pooled from 6 case-control studies in the US, Canada, UK, and New Zealand within the International Lung Cancer Consortium. Study-specific associations between cannabis smoking and lung cancer were estimated using unconditional logistic regression adjusting for sociodemographic factors, tobacco smoking status and pack-years; odds-ratio estimates were pooled using random effects models. Subgroup analyses were done for sex, histology and tobacco smoking status. The shapes of dose-response associations were examined using restricted cubic spline regression. The overall pooled OR for habitual versus nonhabitual or never users was 0.96 (95% CI: 0.66-1.38). Compared to nonhabitual or never users, the summary Odds Ratio was 0.88 (95%CI: 0.63-1.24) for individuals who smoked 1 or more joint-equivalents of cannabis per day and 0.94 (95%CI: 0.67-1.32) for those consumed at least 10 joint-years. For adenocarcinoma cases the ORs were 1.73 (95%CI: 0.75-4.00) and 1.74 (95%CI: 0.85-3.55), respectively. However, no association was found for the squamous cell carcinoma based on small numbers. Weak associations between cannabis smoking and lung cancer were observed in never tobacco smokers. Spline modeling indicated a weak positive monotonic association between cumulative cannabis use and lung cancer, but precision was low at high exposure levels. Results from our pooled analyses provide little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effect for heavy consumption cannot be excluded.

Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience

Waissengrin B1, Urban D2, Leshem Y2, Garty M1, Wolf I3.

1. Institute of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
2. Institute of Oncology, Chaim Sheba Medical Center, Ramat Gan, Israel
3. Institute of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
Electronic address: idow@tlvmc.gov.il

<http://www.ncbi.nlm.nih.gov/pubmed/24937161>

The use of the cannabis plant (*Cannabis sativa* L.) for the palliative treatment of cancer patients has been legalized in multiple jurisdictions including Israel. Yet, not much is currently known regarding the efficacy and patterns of use of cannabis in this setting. To analyze the indications for the administration of cannabis among adult Israeli cancer patients and evaluate its efficacy. Efficacy and patterns of use of cannabis were evaluated using physician-completed application forms, medical files, and a detailed questionnaire in adult cancer patients treated at a single institution.

Of approximately 17,000 cancer patients seen, 279 (<1.7%) received a permit for cannabis from an authorized institutional oncologist. The median age of cannabis users was 60 years (range 19-93 years), 160 (57%) were female, and 234 (84%) had metastatic disease. Of 151 (54%) patients alive at six months, 70 (46%) renewed their cannabis permit. Renewal was more common among younger patients and those with metastatic disease. Of 113 patients alive and using cannabis at one month, 69 (61%) responded to the detailed questionnaire. Improvement in pain, general well-being, appetite, and nausea were reported by 70%, 70%, 60%, and 50%, respectively. Side effects were mild and consisted mostly of fatigue and dizziness.

Cannabis use is perceived as highly effective by some patients with advanced cancer and its administration can be regulated, even by local authorities. Additional studies are required to evaluate the efficacy of cannabis as part of the palliative treatment of cancer patients.

Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study

Degenhardt L1, Lintzeris N2, Campbell G3, Bruno R4, Cohen M5, Farrell M3, Hall WD6.

1. National Drug and Alcohol Research Centre, UNSW, Australia; School of Population and Global Health, University of Melbourne, Australia
2. Discipline of Addiction Medicine, University of Sydney, Australia; The Langton Centre, South East Sydney Local Health District (SESLHD) Drug and Alcohol Services, Australia
3. National Drug and Alcohol Research Centre, UNSW, Australia
4. National Drug and Alcohol Research Centre, UNSW, Australia
School of Medicine, University of Tasmania, Australia
5. St Vincent's Clinical School, UNSW Medicine, UNSW, Australia
6. Centre for Youth Substance Abuse Research, University of Queensland, Australia
National Addiction Centre, Kings College, London, England, UK
Electronic address: l.degenhardt@unsw.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/25533893>

There is increasing debate about cannabis use for medical purposes, including for symptomatic treatment of chronic pain. We investigated patterns and correlates of cannabis use in a large community sample of people who had been prescribed opioids for chronic non-cancer pain.

Cannabis use for pain relief purposes appears common among people living with chronic non-cancer pain, and users report greater pain relief in combination with opioids than when opioids are used alone.

Medical marijuana for digestive disorders: high time to prescribe?

Gerich ME1, Isfort RW1, Brimhall B2, Siegel CA3.

1. Division of Gastroenterology and Hepatology, University of Colorado, Aurora, Colorado, USA
2. Department of Medicine, University of Colorado, Aurora, Colorado, USA
3. Inflammatory Bowel Disease Center, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

<http://www.ncbi.nlm.nih.gov/pubmed/25199471>

The use of recreational and medical marijuana is increasingly accepted by the general public in the United States. Along with growing interest in marijuana use has come an understanding of marijuana's effects on normal physiology and disease, primarily through elucidation of the human endocannabinoid system.

Scientific inquiry into this system has indicated potential roles for marijuana in the modulation of gastrointestinal symptoms and disease. Some patients with gastrointestinal disorders already turn to marijuana for symptomatic relief, often without a clear understanding of the risks and benefits of marijuana for their condition. Unfortunately, that lack of understanding is shared by health-care providers.

Marijuana's federal legal status as a Schedule I controlled substance has limited clinical investigation of its effects. There are also potential legal ramifications for physicians who provide recommendations for marijuana for their patients. Despite these constraints, as an increasing number of patients consider marijuana as a potential therapy for their digestive disorders, health-care providers will be asked to discuss the issues surrounding medical marijuana with their patients.

Online survey characterizing vaporizer use among cannabis users

Lee DC1, Crosier BS2, Borodovsky JT2, Sargent JD3, Budney AJ2.

1,2. Department of Psychiatry, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

3. C. Everett Koop Institute, Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH, USA

Electronic address: Dustin.C.Lee@Dartmouth.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/26774946>

Along with changes in cannabis laws in the United States and other countries, new products for consuming cannabis are emerging, with unclear public health implications. Vaporizing or “vaping” cannabis is gaining popularity, but little is known about its prevalence or consequences.

This study characterized the prevalence and current patterns of vaping cannabis among a large national sample of cannabis users. An online survey was distributed through Facebook ads targeting individuals with interests related to cannabis use. The sample comprised 2910 cannabis users (age: 18-90, 84% male, 74% Caucasian).

A majority (61%) endorsed lifetime prevalence of ever vaping, 37% reported vaping in the past 30 days, 20% reported vaping more than 100 lifetime days, and 12% endorsed vaping as their preferred method. Compared to those that had never vaped, vaporizer users were younger, more likely to be male, initiated cannabis at an earlier age, and were less likely to be African American. Those that preferred vaping reported it to be healthier, better tasting, produced better effects, and more satisfying. Only 14% reported a reduction in smoking cannabis since initiating vaping, and only 5% mixed cannabis with nicotine in a vaporizer. Many cannabis users report vaping cannabis, but currently only a small subset prefers vaping to smoking and reports frequent vaping.

Urology • February 2015

Association between cannabis use and the risk of bladder cancer: results from the California Men's Health Study

Thomas AA1, Wallner LP2, Quinn VP2, Slezak J2, Van Den Eeden SK3, Chien GW4, Jacobsen SJ2.

1. Department of Urology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA
2. Department of Research and Evaluation, Kaiser Permanente Southern California, Los Angeles, CA
3. Division of Research, Kaiser Permanente Northern California, Oakland, CA
4. Department of Urology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA
Electronic address: anil.a.thomas@kp.org

<http://www.ncbi.nlm.nih.gov/pubmed/25623697>

To investigate the association of cannabis use and tobacco smoking on the incidence of bladder cancer within the California Men's Health Study cohort. Although a cause and effect relationship has not been established, cannabis use may be inversely associated with bladder cancer risk in this population.

Proceedings Of The National Academy Of Science USA • February 2015

Beliefs modulate the effects of drugs on the human brain

Volkow ND1, Baler R2.

1,2. National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD
nvolkow@nida.nih.gov

Full text with 34 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1166590/>

Convergent neurobiological studies of value-based learning, and the computational models that flow from them, have long pointed to the existence of a reciprocal relationship between dopamine and beliefs. The complex interactions between the pharmacological (reinforcing) effects of addictive drugs and the conditioned responses (expectations) engendered by their continued use (1, 2) provide some of the most compelling examples of this dialogue between molecules and cognition. They help explain, among others, why drug abusers perceive the drug as more pleasurable when they expect it relative to when they do not (3, 4). The report by Gu et al. in PNAS (5) represents an important step forward in this context because it offers new insights into how the power of belief modulates nicotine-driven learning signals related to nondrug rewards (money), as well as non-drug-related decisions (choice behavior). More specifically, this work illuminates the mechanisms whereby belief can influence nonconscious learned association by modulating how the brain performs risk decisions while under the effects of nicotine.

Are cannabidiol and $\Delta(9)$ -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review

McPartland JM1, Duncan M, Di Marzo V, Pertwee RG.

1. Division of Molecular Biology, GW Pharmaceuticals, Salisbury, Wiltshire, UK

Full text with 123 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4301686/>

Based upon evidence that the therapeutic properties of Cannabis preparations are not solely dependent upon the presence of $\Delta(9)$ -tetrahydrocannabinol (THC), pharmacological studies have been recently carried out with other plant cannabinoids (phytocannabinoids), particularly cannabidiol (CBD) and $\Delta(9)$ -tetrahydrocannabivarin (THCV). Results from some of these studies have fostered the view that CBD and THCV modulate the effects of THC via direct blockade of cannabinoid CB1 receptors, thus behaving like first-generation CB1 receptor inverse agonists, such as rimonabant. Here, we review in vitro and ex vivo mechanistic studies of CBD and THCV, and synthesize data from these studies in a meta-analysis. Synthesized data regarding mechanisms are then used to interpret results from recent pre-clinical animal studies and clinical trials. The evidence indicates that CBD and THCV are not rimonabant-like in their action and thus appear very unlikely to produce unwanted CNS effects. They exhibit markedly disparate pharmacological profiles particularly at CB1 receptors: CBD is a very low-affinity CB1 ligand that can nevertheless affect CB1 receptor activity in vivo in an indirect manner, while THCV is a high-affinity CB1 receptor ligand and potent antagonist in vitro and yet only occasionally produces effects in vivo resulting from CB1 receptor antagonism. THCV has also high affinity for CB2 receptors and signals as a partial agonist, differing from both CBD and rimonabant. These cannabinoids illustrate how in vitro mechanistic studies do not always predict in vivo pharmacology and underlie the necessity of testing compounds in vivo before drawing any conclusion on their functional activity at a given target.

This report synthesizes the reports on the following page

Landmark 20th Century Studies regarding the effects of CBD upon THC

Animal Studies

CBD combined with isomeric tetrahydrocannabinols caused 'synergistic hypnotic activity in the mouse' – Loewe and Modell, 1941
CBD inhibited THC effects on mouse catatonia, rat ambulation and rat aggression, but potentiated THC effects on mouse analgesia and rat rope climbing – Karniol and Carlini, 1973
CBD decreased THC suppression of behaviour in rats and pigeons – Davis and Borgen, 1974
CBD potentiated THC-induced changes in hepatic enzymes – Poddar et al., 1974
CBD increased THC potentiation of hexobarbitone in rats – Fernandes et al., 1974
CBD increased THC reduction of intestinal motility in mice – Anderson et al., 1974
CBD reduced THC hypothermia and bradycardia – Borgen and Davis, 1974
CBD blocked THC inhibition of pig brain monamine oxidase – Schurr and Livne, 1976
CBD antagonized THC antinociceptive effects in mice – Welburn et al., 1976
CBD prevented tonic and clonic convulsions induced by THC – Consroe et al., 1977
CBD antagonized THC suppression of operant behaviour in monkeys – Brady and Balster, 1980
CBD delayed THC discriminative effects – Zuardi et al., 1981
CBD prolonged THC cue effects in rats – Hiltunen and Järbe, 1986
CBD antagonized THC catalepsy in mice – Formukong et al., 1988a
CBD increased THC analgesic activity and anti-erythema – Formukong et al., 1988b
CBD prolonged and reduced the hydroxylation of THC – Bornheim et al., 1995, 1998

Human clinical trials

CBD decreased anxiety caused by THC – Karniol et al., 1974
CBD slightly increased time to onset, intensity and duration of THC intoxication – Hollister and Gillespie, 1975

CBD attenuated THC euphoria – Dalton et al., 1976
CBD reduced anxiety provoked by THC – Zuardi et al., 1982
CBD improved sleep and decreased epilepsy – Cunha et al., 1980; Carlini and Cunha, 1981
CBD decreased cortisol secretion and had sedative effects – Zuardi et al., 1993
CBD provided antipsychotic benefits – Zuardi et al., 1995

Landmark 21st Century In Vivo Studies of CBD functional antagonism of THC

Animal studies

CBD antagonized THC-induced spatial memory – Fadda et al., 2004
CBD reversed THC-induced conditioned place aversion – Vann et al., 2008
CBD reversed THC-induced decrease in social interaction – Malone et al., 2009
CBD increased hippocampal cell survival and neurogenesis, whereas THC has the opposite effect; the CBD response is absent in CB1^{-/-} knockout mice – Wolf et al., 2010

Human clinical trials and epidemiology studies

CBD reduced THC intoxication and impairment in binocular depth perception (a model of psychosis) – Leweke et al., 2000
Sativexa compared to THC alone reduced adverse effects in patients with multiple sclerosis – Wade et al., 2003; Zijicsek et al., 2003
CBD counteracted THC somnolence and morning-after memory deficits – Nicholson et al., 2004.
High-THC cannabis with higher dose of CBD caused less anxiety than high-THC cannabis with lower dose of CBD – Ilan et al., 2005
No difference in appetite and quality of life (QOL) scores between cannabis extract and THC alone – Strasser et al., 2006
Increased CBD-to-THC ratios in chronic cannabis users inversely correlated with expression of psychotic symptoms – Morgan and Curran, 2008
CBD reduced anxiety, skin conductance response and amygdala activity – the opposite of THC effects – Fusar-Poli et al., 2009
CBD reduced 'psychotic scores' of THC – Bhattacharyya et al., 2010

CBD attenuated the appetitive effects of THC – Morgan et al., 2010a
Increased CBD-to-THC ratios in chronic cannabis users correlated with a reduction of cognitive and memory deficits – Morgan et al., 2010a
Increased CBD-to-THC ratios in chronic cannabis users inversely correlated with liking for drug-related stimuli including food – Morgan et al., 2010b
Increased CBD-to-THC ratio is associated with lower degrees of negative psychiatric symptoms – Schubart et al., 2011
No difference in side effect profile between cannabis extract and THC alone – Karschner et al., 2011b
Increased CBD-to-THC ratios in chronic cannabis users inversely correlated with volume loss in the hippocampus – Demirakca et al., 2011
CBD inhibited THC-elicited paranoid symptoms and hippocampal-dependent memory impairment – Englund et al., 2013

Landmark 21st Century Studies of CBD potentiating the effects of THC

Animal studies

CBD potentiated THC antinociception – Varvel et al., 2006
CBD enhanced THC tetrad effects – Hayakawa et al., 2008
CBD turned an ineffective THC dose into an effective one in colitis – Jamontt et al., 2010
CBD altered THC pharmacokinetics and augments some THC behavioural effects – Klein et al., 2011
Sativex compared to THC alone enhanced antinociception in a rat model of neuropathic pain – Comelli et al., 2008

Human clinical trials and epidemiology studies

CBD plus THC imparted synergistic inhibition of human glioblastoma cancer cell growth and apoptosis – Marcu et al., 2010
Sativexa compared to THC alone provides greater pain relief and improvement in sleep – Notcutt et al., 2004
Sativexa compared to THC extract reduced cancer-related pain – Johnson et al., 2010
Sativexa compared to THC alone reduced abnormalities in psychomotor performance associated with schizophrenia – Roser et al., 2009

Assessing the Effects of Medical Marijuana Laws on Marijuana Use: The Devil is in the Details

1. Rosalie Liccardo Pacula, Ph.D., David Powell, Ph.D., Paul Heaton, Ph.D., and Eric L. Sevigny, Ph.D.

1. RAND Corporation and National Bureau of Economic Research

Full text with 41 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315233/>

This paper sheds light on previous inconsistencies identified in the literature regarding the relationship between medical marijuana laws (MMLs) and recreational marijuana use by closely examining the importance of policy dimensions (registration requirements, home cultivation, dispensaries) and the timing of when particular policy dimensions are enacted. Using data from our own legal analysis of state MMLs, we evaluate which features are associated with adult and youth recreational and heavy use by linking these policy variables to data from the Treatment Episodes Data System (TEDS) and the National Longitudinal Survey of Youth (NLSY97). We employ differences-in-differences techniques, controlling for state and year fixed effects, allowing us to exploit within-state policy changes. We find that while simple dichotomous indicators of MML laws are not positively associated with marijuana use or abuse, such measures hide the positive influence legal dispensaries have on adult and youth use, particularly heavy use. Sensitivity analyses that help address issues of policy endogeneity and actual implementation of dispensaries support our main conclusion that not all MML laws are the same. Dimensions of these policies, in particular legal protection of dispensaries, can lead to greater recreational marijuana use and abuse among adults and those under the legal age of 21 relative to medical marijuana laws without this supply source.

Electronic cigarettes and cannabis: an exploratory study

By J.F. Etter

Institute of Global Health, Faculty of Medicine, University of Geneva, Geneva, Switzerland

<http://www.ncbi.nlm.nih.gov/pubmed/25613866>

To describe cannabis 'vaping' with electronic cigarettes (e-cigarettes) or electronic vaporizers (e-vaporizers).

Internet survey in 2013-2014. Participants were 11 people who 'vaped' cannabis with e-cigarettes and 44 people who vaped cannabis with e-vaporizers, enrolled online.

Most participants were men (78%). They had used e-cigarettes for 6 days and e-vaporizers for 50 days on average to vape cannabis. Current users of e-cigarettes vaped cannabis on 2 days/week versus 6 days/week for users of e-vaporizers. In these devices, they mostly inserted cannabis buds and oil rather than hashish or wax/butane honey oil. Dual users, who both smoked and vaped cannabis, currently smoked 5 joints/week compared to 14 joints/week before they started to vape cannabis ($p = 0.004$). Half the participants (45%) reported that vaping cannabis helped them stop or reduce their total cannabis use, 37% that it had no impact on their cannabis use, and 6% that it increased it. Vaping cannabis was perceived as healthier and more discrete than smoking it (less odor). Disadvantages included dry mouth and fewer positive cannabis effects. Cannabis vaping via e-cigarettes or e-vaporizers is an infrequent behavior that was previously almost undocumented.

E-cigarettes do not appear to be a very appealing way to use cannabis.

Prenatal marijuana exposure predicts marijuana use in young adulthood

Sonon KE1, Richardson GA2, Cornelius JR3, Kim KH4, Day NL5.

1. Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, 130 DeSoto Street, Pittsburgh, PA 15260, USA
2. Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA
3. Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA
4. Department of Psychology in Education, School of Education, 5930 Wesley W. Posvar Hall, Pittsburgh, PA 15260, USA
5. Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA
Electronic address: kristen.sonon@gmail.com

Full text with 39 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4381999/>

Studies have reported effects of prenatal marijuana exposure (PME) on cognitive and behavioral outcomes. An earlier publication from this study found that PME predicted early onset of marijuana use and frequency of marijuana use at age 14. No study has reported the effects of PME on marijuana use in young adulthood. This is a developmental period when substance use peaks, and by which, initiation of substance use has largely occurred.

PME predicted marijuana use in the offspring at 22 years after controlling for significant covariates. Prenatal alcohol exposure, offspring race, gender, and age were also significant predictors, but family history of substance abuse or disorder, and sociodemographic and psychological characteristics of the mother and offspring were not. This association was not moderated by gender or race.

PME is associated with subsequent marijuana use in young adulthood after considering the effects of other significant factors. These findings have important implications for public health given the recent trend toward legitimization of marijuana use.

Medical Marijuana programs: implications for cannabis control policy—observations from Canada

Fischer B1, Kuganesan S2, Room R3.

1. Centre for Applied Research in Mental Health and Addiction, Faculty of Health Sciences, Simon Fraser University, 2400 - 515 West Hastings St., Vancouver, Canada
Social & Epidemiological Research Department, Centre for Addiction and Mental Health, 33 Russell St., Toronto, Canada
Department of Psychiatry, University of Toronto, 250 College St., Toronto, Canada
2. Social & Epidemiological Research Department, Centre for Addiction and Mental Health, 33 Russell St., Toronto, Canada
3. Centre for Alcohol Policy Research, Turning Point, Fitzroy, Victoria 3065, Australia
Melbourne School of Population and Global Health, University of Melbourne, 207 Bouverie Street, Victoria 3010, Australia
Centre for Social Research on Alcohol & Drugs, Stockholm University, SE-106 91 Stockholm, Sweden
Electronic address: bfischer@sfu.ca

<http://www.ncbi.nlm.nih.gov/pubmed/25287942>

While prohibition has been the dominant regime of cannabis control in most countries for decades, an increasing number of countries have been implementing cannabis control reforms recently, including decriminalization or even legalization frameworks. Canada has held out from this trend, although it has among the highest cannabis use rates in the world.

Cannabis use is universally criminalized, and the current (conservative) federal government has vowed not to implement any softening reforms to cannabis control. As a result of several higher court decisions, the then federal government was forced to implement a 'medical marijuana access regulations' program in 2001 to allow severely ill patients therapeutic use and access to therapeutic cannabis while shielding them from prosecution. The program's regulations and approval processes were complex and subject to extensive criticism; initial uptake was low and most medical marijuana users continued their use and supply outside the program's auspices.

This year, the government introduced new 'marijuana for medical purposes regulations', which allow physicians to 'authorize' medical marijuana use for virtually any health condition for which this is considered beneficial; supply is facilitated by licensed commercial producers. It is expected that some 500,000 users, and dozens of commercial producers will soon be approved under the program, arguably constituting - as with medical marijuana schemes elsewhere, e.g. in California--de facto 'legalization'. We discuss the question whether the evolving scope and realities of 'medical cannabis' provisions in Canada offer a 'sneaky side door' or a 'better third way' to cannabis control reform, and what the potential wider implications are of these developments.

Cancer Cytopathology • January 2015

**Cannabis conundrum: evidence of harm?:
Opposition to marijuana use is often rooted in arguments about the drug's harm to children and adults,
but the scientific evidence is seldom clear-cut**

By B. Nelson

Full text, PDF with 8 references

<http://onlinelibrary.wiley.com/doi/10.1002/cncy.21516/epdf>



**Cannabis Conundrum:
Evidence of Harm?**

Opposition to marijuana use is often rooted in arguments about the drug's harm to children and adults, but the scientific evidence is seldom clear-cut

Endocannabinoid signalling and the deteriorating brain

Di Marzo V1, Stella N2, Zimmer A3.

1. Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, 80078 Pozzuoli, Naples, Italy

2. Department of Pharmacology, University of Washington

Department of Psychiatry and Behavioral Science, University of Washington, 1959 Pacific Avenue North, Seattle, Washington 98103, USA

3. Institute for Molecular Psychiatry, University of Bonn, Sigmund Freud Straße 25, Bonn 53127, Germany

Full text with 154 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471876/>

Ageing is characterized by the progressive impairment of physiological functions and increased risk of developing debilitating disorders, including chronic inflammation and neurodegenerative diseases. These disorders have common molecular mechanisms that can be targeted therapeutically. In the wake of the approval of the first cannabinoid-based drug for the symptomatic treatment of multiple sclerosis, we examine how endocannabinoid (eCB) signalling controls—and is affected by—normal ageing and neuroinflammatory and neurodegenerative disorders. We propose a conceptual framework linking eCB signalling to the control of the cellular and molecular hallmarks of these processes, and categorize the key components of endocannabinoid signalling that may serve as targets for novel therapeutics.

Age-related changes at different system levels and their regulation by endocannabinoid signalling

Ageing is accompanied by changes in cellular processes, impairments in the integration of cellular activities, and deficits in physiological functions. a | At the cellular level, important hallmarks of ageing in the CNS are impairments in mitochondrial functions, disruption of proteostasis and autophagy, and alterations in signalling pathways involved in nutrient sensing, such as the mammalian target of rapamycin (mTOR) pathway. Endocannabinoids (eCBs) act as intracellular signalling molecules that modulate mitochondrial activity through cannabinoid type 1 (CB1) receptors located either in the plasma membrane or on lysosomes (l-CB1) and possibly mitochondria (m-CB1). In particular, activation of m-CB1 seems to reduce mitochondrial respiration, and to decrease mitochondrial cyclic AMP levels and protein kinase A

(PKA) activity¹¹¹. CB1 receptors located on lysosomes enhance the intracellular release of Ca²⁺, increase the permeability of lysosomes and the release of cathepsin D. CB1 receptors on the cell surface also stimulate mTOR signalling, through an Akt-dependent mechanism, resulting in an enhanced activity of phosphoprotein 70 ribosomal protein S6 kinase (p70S6K). The mechanism by which cannabinoids stimulate autophagy is not entirely clear (indicated by a question mark), and is probably independent of mTOR. b | At the tissue level, disruption of intercellular communication is another hallmark of ageing. Endocannabinoids are best known as signalling molecules for short-range cell–cell communication. At synapses they provide a retrograde feedback system, in which activation of presynaptic CB1 receptors reduces neurotransmitter release probability. Endocannabinoids also modulate the activity of astrocytes and microglia. These cells may also be a source for brain endocannabinoids (eCBs). Increased numbers of activated microglia and astrocytes are typically found in the ageing brain and result in an increased production of pro-inflammatory cytokines (PICs). This process leads to a change towards a more pro-inflammatory milieu in the brain. c | At the organism level, eCBs modulate the activity of several systems that are important in ageing, such as metabolic processes or hypothalamic activity. Cannabinoids are generally protective against age-related pathologies, including neuroinflammation and neurodegeneration. They also protect against some age-related pathologies outside the CNS, such as osteoporosis⁵⁸. Akt, serine/threonine Akt; DAG, diacylglycerol; DAGLs, diacylglycerol lipases; DSI, depolarization-induced suppression of inhibitory neurotransmission; Glu, Glutamate; IC, intracellular; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; PKA, protein kinase A; TRP, transient receptor potential channel.



CANNABIS • 2014 PEER REVIEW

Use and medicalization of marihuana in cancer patients

Pedro E, Rodríguez FM.

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Anecdotal reports and some clinical studies suggest that marihuana (*Cannabis sativa*) is effective in treating a variety of conditions such as glaucoma, migraine, pain, spasticity of multiple sclerosis, anorexia, insomnia, depression, nausea and vomiting. One of the diseases mostly associated to a beneficial effect from marihuana is cancer. Twenty-one states of the United States including the District of Columbia have approved the use of marihuana for cancer and other medical conditions. In Puerto Rico, public debate on criminal penalty removal and medicalization of marihuana has intensified. It is considered essential for health professionals to have strong scientific evidence on the effectiveness and safety of medications or substances when recommending them for treating illness. This article discusses scientific evidence and information provided by prestigious organizations on the effectiveness and safety of marihuana and its derivatives in cancer patients.

Legalizing Cannabis: A physician's primer on the pulmonary effects of marijuana

Lutchmansingh D1, Pawar L1, Savici D1.

Division of Pulmonary and Critical Care Medicine, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210 USA

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226845/>

Habitual smoking of marijuana is associated with multiple respiratory symptoms such as cough, sputum production, and wheezing. These symptoms are not significantly different from those exhibited by tobacco smokers. Furthermore, endobronchial biopsies of habitual smokers of marijuana and /or tobacco have shown that both marijuana and cigarette smoking cause significant bronchial mucosal histopathology and that these effects are additive. Although marijuana smokers have minimal changes in pulmonary function studies as compared to tobacco smokers, they may develop bullous disease and spontaneous pneumothoraces. The relationship between marijuana smoking and lung cancer remains unclear due to design limitations of the studies published so far. These findings should warn individuals that marijuana smoking may result in serious short-term and long-term respiratory complications, and habitual marijuana use should be viewed with caution. The medical literature so far does not support routine evaluation by pulmonary function tests or imaging studies; until more definitive data is available, we do not recommend the regular use of these tests in the evaluation of habitual marijuana smokers.

Epilepsy Behavior • December 2014

Cannabis, cannabidiol, and epilepsy—from receptors to clinical response

Szaflarski JP1, Bebin EM2.

1,2. UAB Epilepsy Center, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
Electronic address: szaflaj@uab.edu.

<http://www.ncbi.nlm.nih.gov/pubmed/25282526>

Recreational cannabis use in adults with epilepsy is widespread. The use of cannabis for medicinal purposes is also becoming more prevalent. For this purpose, various preparations of cannabis of varying strengths and content are being used. The recent changes in the legal environment have improved the availability of products with high cannabidiol (CBD) and low tetrahydrocannabinol (THC) concentrations. There is some anecdotal evidence of their potential efficacy, but the mechanisms of such action are not entirely clear. Some suspect an existence of synergy or “entourage effect” between CBD and THC. There is strong evidence that THC acts via the cannabinoid receptor CB1. The mechanism of action of CBD is less clear but is likely polypharmacological. The scientific data support the role of the endocannabinoid system in seizure generation, maintenance, and control in animal models of epilepsy. There are clear data for the negative effects of cannabis on the developing and mature brain though these effects appear to be relatively mild in most cases. Further data from well-designed studies are needed regarding short- and long-term efficacy and side effects of CBD or high-CBD/low-THC products for the treatment of seizures and epilepsy in children and adults.

Expert Reviews In Neurotherapy • December 2014

Medical marijuana in neurology

Benbadis SR1, Sanchez-Ramos J, Bozorg A, Giarratano M, Kalidas K, Katzin L, Robertson D, Vu T, Smith A, Zesiewicz T.

Department of Neurology, University of South Florida, Tampa, FL, USA

<http://www.ncbi.nlm.nih.gov/pubmed/25427150>

Constituents of the Cannabis plant, cannabinoids, may be of therapeutic value in neurologic diseases. The most abundant cannabinoids are $\Delta(9)$ -tetrahydrocannabinol, which possesses psychoactive properties, and cannabidiol, which has no intrinsic psychoactive effects, but exhibits neuroprotective properties in preclinical studies. A small number of high-quality clinical trials support the safety and efficacy of cannabinoids for treatment of spasticity of multiple sclerosis, pain refractory to opioids, glaucoma, nausea and vomiting. Lower level clinical evidence indicates that cannabinoids may be useful for dystonia, tics, tremors, epilepsy, migraine and weight loss. Data are also limited in regards to adverse events and safety. Common nonspecific adverse events are similar to those of other CNS 'depressants' and include weakness, mood changes and dizziness. Cannabinoids can have cardiovascular adverse events and, when smoked chronically, may affect pulmonary function. Fatalities are rare even with recreational use. There is a concern about psychological dependence, but physical dependence is less well documented. Cannabis preparations may presently offer an option for compassionate use in severe neurologic diseases, but at this point, only when standard-of-care therapy is ineffective. As more high-quality clinical data are gathered, the therapeutic application of cannabinoids will likely expand.

CA: A Cancer Journal For Clinicians • December 2014

Medical marijuana for cancer

By Joan L. Kramer, MD

Medical Editor, American Cancer Society, Atlanta, GA
joan.kramer@cancer.org

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Marijuana has been used for centuries, and interest in its medicinal properties has been increasing in recent years. Investigations into these medicinal properties has led to the development of cannabinoid pharmaceuticals such as dronabinol, nabilone, and nabiximols. Dronabinol is best studied in the treatment of nausea secondary to cancer chemotherapy and anorexia associated with weight loss in patients with acquired immune deficiency syndrome, and is approved by the US Food and Drug Administration for those indications. Nabilone has been best studied for the treatment of nausea secondary to cancer chemotherapy. There are also limited studies of these drugs for other conditions. Nabiximols is only available in the United States through clinical trials, but is used in Canada and the United Kingdom for the treatment of spasticity secondary to multiple sclerosis and pain. Studies of marijuana have concentrated on nausea, appetite, and pain. This article will review the literature regarding the medical use of marijuana and these cannabinoid pharmaceuticals (with emphasis on indications relevant to oncology), as well as available information regarding adverse effects of marijuana use.

Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychoactive cannabinoid

Borrelli F1, Pagano E1, Romano B1, Panzera S1, Maiello F2, Coppola D2, De Petrocellis L3, Buono L3, Orlando P4, Izzo AA5.

1. Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy
Department of Diagnostic Services (Anatomy and Pathologic Histology Service), Ospedale dei Pellegrini, ASL 1, 80135 Naples, Italy
Institute of Biomolecular Chemistry, National Research Council, Via Campi Flegrei 34, 80078 Pozzuoli, Naples, Italy
and Institute of Protein Biochemistry, National Research Council, Via P. Castellino 111, 80131 Naples, Italy
2. Department of Diagnostic Services (Anatomy and Pathologic Histology Service), Ospedale dei Pellegrini, ASL 1, 80135 Naples, Italy
3. Institute of Biomolecular Chemistry, National Research Council, Via Campi Flegrei 34, 80078 Pozzuoli, Naples, Italy
4. Institute of Protein Biochemistry, National Research Council, Via P. Castellino 111, 80131 Naples, Italy
5. Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy
Department of Diagnostic Services (Anatomy and Pathologic Histology Service), Ospedale dei Pellegrini, ASL 1, 80135 Naples, Italy
Institute of Biomolecular Chemistry, National Research Council, Via Campi Flegrei 34, 80078 Pozzuoli, Naples, Italy
Institute of Protein Biochemistry, National Research Council, Via P. Castellino 111, 80131 Naples, Italy

aaizzo@unina.it.

Full text, PDF, with 62 references

<http://carcin.oxfordjournals.org/content/35/12/2787.full.pdf>

Cannabigerol (CBG) is a safe non-psychoactive Cannabis-derived cannabinoid (CB), which interacts with specific targets involved in carcinogenesis.

Specifically, CBG potently blocks transient receptor potential (TRP) M8 (TRPM8), activates TRPA1, TRPV1 and TRPV2 channels, blocks 5-hydroxytryptamine receptor 1A (5-HT1A) receptors and inhibits the reuptake of endocannabinoids. Here, we investigated whether CBG protects against colon tumorigenesis. Cell growth was evaluated in colorectal cancer (CRC) cells using the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide and 3-amino-7-dimethylamino-2-methylphenazine hydrochloride assays; apoptosis was examined by histology and by assessing caspase 3/7 activity; reactive oxygen species (ROS) production by a fluorescent probe; CB receptors, TRP and CCAAT/enhancer-binding protein homologous protein (CHOP) messenger RNA (mRNA) expression were quantified by reverse transcription-polymerase chain reac-

tion; small hairpin RNA-vector silencing of TRPM8 was performed by electroporation. The in vivo antineoplastic effect of CBG was assessed using mouse models of colon cancer. CRC cells expressed TRPM8, CB1, CB2, 5-HT1A receptors, TRPA1, TRPV1 and TRPV2 mRNA. CBG promoted apoptosis, stimulated ROS production, upregulated CHOP mRNA and reduced cell growth in CRC cells. CBG effect on cell growth was independent from TRPA1, TRPV1 and TRPV2 channels activation, was further increased by a CB2 receptor antagonist, and mimicked by other TRPM8 channel blockers but not by a 5-HT1A antagonist. Furthermore, the effect of CBG on cell growth and on CHOP mRNA expression was reduced in TRPM8 silenced cells. In vivo, CBG inhibited the growth of xenograft tumours as well as chemically induced colon carcinogenesis. **CBG hampers colon cancer progression in vivo and selectively inhibits the growth of CRC cells, an effect shared by other TRPM8 antagonists. CBG should be considered translationally in CRC prevention and cure.**

Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations

Kahan M1, Srivastava A2, Spithoff S3, Bromley L4.

1. Associate Professor in the Department of Family and Community Medicine at the University of Toronto in Ontario and Medical Director of the Substance Use Service at Women's College Hospital
2. Assistant Professor and Research Scholar in the Department of Family and Community Medicine at the University of Toronto and a staff physician with the St Joseph's Health Centre Family Health Team
3. Staff physician with the Women's College Hospital Family Health Team
4. Staff physician at Sandy Hill Community Health Centre in Ottawa, Canada
meldon.kahan@wchospital.ca

Full text with 89 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264803/>

To offer preliminary guidance on prescribing smoked cannabis for chronic pain before the release of formal guidelines.

We reviewed the literature on the analgesic effectiveness of smoked cannabis and the harms of medical and recreational cannabis use. We developed recommendations on indications, contraindications, precautions, and dosing of smoked cannabis, and categorized the recommendations based on levels of evidence. Evidence is mostly level II (well conducted observational studies) and III (expert opinion).

Smoked cannabis might be indicated for patients with severe neuropathic pain conditions who have not responded to adequate trials of pharmaceutical cannabinoids and standard analgesics (level II evidence). Smoked cannabis is contraindicated in patients who are 25 years of age or younger (level II evidence); who have a current, past, or strong family history of psychosis (level II evidence); who have a current or past cannabis use disorder (level III evidence); who have a current substance use disorder (level III evidence); who have cardiovascular or respiratory disease (level III evidence); or who are pregnant or planning to become pregnant (level II evidence). It should be used with caution in patients who smoke tobacco (level II evidence), who are at increased risk of cardiovascular disease (level III evidence), who have anxiety or mood disorders (level II evidence), or who are taking higher doses of opioids or benzodiazepines (level III evidence). Cannabis users should be advised not to drive for at least 3 to 4 hours after smoking, for at least 6 hours after oral ingestion, and for at least 8 hours if they experience a subjective "high" (level II evidence). The maximum recommended dose is 1 inhalation 4 times per day (approximately 400 mg per day) of dried cannabis containing 9% delta-9-tetrahydrocannabinol (level III evidence). Physicians should avoid referring patients to "cannabinoid" clinics (level III evidence).

Future guidelines should be based on systematic review of the literature on the safety and effectiveness of smoked cannabis. Further research is needed on the effectiveness and long-term safety of smoked cannabis compared with pharmaceutical cannabinoids, opioids, and other standard analgesics.

Down-regulation of cyclooxygenase-2 (COX-2) by cannabidiolic acid in human breast cancer cells

Takeda S1, Okazaki H, Ikeda E, Abe S, Yoshioka Y, Watanabe K, Aramaki H.

Department of Molecular Biology, Daiichi University of Pharmacy

Full text, PDF, with 41 references

https://www.jstage.jst.go.jp/article/jts/39/5/39_711/_pdf

Metastases are known to be responsible for approximately 90% of breast cancer-related deaths. Cyclooxygenase-2 (COX-2) is involved not only in inflammatory processes, but also in the metastasis of cancer cells; it is expressed in 40% of human invasive breast cancers. To comprehensively analyze the effects of cannabidiolic acid (CBDA), a selective COX-2 inhibitor found in the fiber-type cannabis plant (Takeda et al., 2008), on COX-2 expression and the genes involved in metastasis, we performed a DNA microarray analysis of human breast cancer MDA-MB-231 cells, which are invasive breast cancer cells that express high levels of COX-2, treated with CBDA for 48 hr at 25 μ M. The results obtained revealed that COX-2 and Id-1, a positive regulator of breast cancer metastasis, were down-regulated (0.19-fold and 0.52-fold, respectively), while SHARP1 (or BHLHE41), a suppressor of breast cancer metastasis, was up-regulated (1.72-fold) and CHIP (or STUB1) was unaffected (1.03-fold). These changes were confirmed by real-time RT-PCR analyses. Taken together, the results obtained here demonstrated that i) CBDA had dual inhibitory effects on COX-2 through down-regulation and enzyme inhibition, and ii) CBDA may possess the ability to suppress genes that are positively involved in the metastasis of cancer cells in vitro.

Cannabinoid-induced changes in respiration of brain mitochondria

Fišar Z1, Singh N2, Hroudová J3.

1,2,3. Department of Psychiatry, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Ke Karlovu 11, Prague 2 120 00, Czech Republic
Electronic address: zfishar@lf1.cuni.cz.

<http://www.ncbi.nlm.nih.gov/pubmed/25195527>

Cannabinoids exert various biological effects that are either receptor-mediated or independent of receptor signaling. Mitochondrial effects of cannabinoids were interpreted either as non-receptor-mediated alteration of mitochondrial membranes, or as indirect consequences of activation of plasma membrane type 1 cannabinoid receptors (CB1). Recently, CB1 receptors were confirmed to be localized to the membranes of neuronal mitochondria, where their activation directly regulates respiration and energy production. Here, we performed in-depth analysis of cannabinoid-induced changes of mitochondrial respiration using both an antagonist/inverse agonist of CB1 receptors, AM251 and the cannabinoid receptor agonists, $\Delta(9)$ -tetrahydrocannabinol (THC), cannabidiol, anandamide, and WIN 55,212-2. Relationships were determined between cannabinoid concentration and respiratory rate driven by substrates of complex I, II or IV in pig brain mitochondria. Either full or partial inhibition of respiratory rate was found for the tested drugs, with an IC50 in the micromolar range, which verified the significant role of non-receptor-mediated mechanism in inhibiting mitochondrial respiration. Effect of stepwise application of THC and AM251 evidenced protective role of AM251 and corroborated the participation of CB1 receptor activation in the inhibition of mitochondrial respiration. We proposed a model, which includes both receptor- and non-receptor-mediated mechanisms of cannabinoid action on mitochondrial respiration. This model explains both the inhibitory effect of cannabinoids and the protective effect of the CB1 receptor inverse agonist.

The Cannabis Pathway to Non-Affective Psychosis may Reflect Less Neurobiological Vulnerability

Løberg EM1, Helle S2, Nygård M3, Berle JØ2, Kroken RA2, Johnsen E4.

1,4. Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

Department of Clinical Psychology, University of Bergen, Bergen, Norway

2. Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

3. Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway

<http://www.ncbi.nlm.nih.gov/pubmed/25477825>

There is a high prevalence of cannabis use reported in non-affective psychosis. Early prospective longitudinal studies conclude that cannabis use is a risk factor for psychosis, and neurochemical studies on cannabis have suggested potential mechanisms for this effect. Recent advances in the field of neuroscience and genetics may have important implications for our understanding of this relationship. Importantly, we need to better understand the vulnerability \times cannabis interaction to shed light on the mediators of cannabis as a risk factor for psychosis. Thus, the present study reviews recent literature on several variables relevant for understanding the relationship between cannabis and psychosis, including age of onset, cognition, brain functioning, family history, genetics, and neurological soft signs (NSS) in non-affective psychosis. Compared with non-using non-affective psychosis, the present review shows that there seem to be fewer stable cognitive deficits in patients with cannabis use and psychosis, in addition to fewer NSS and possibly more normalized brain functioning, indicating less neurobiological vulnerability for psychosis. There are, however, some familiar and genetic vulnerabilities present in the cannabis psychosis group, which may influence the cannabis pathway to psychosis by increasing sensitivity to cannabis. Furthermore, an earlier age of onset suggests a different pathway to psychosis in the cannabis-using patients. Two alternative vulnerability models are presented to integrate these seemingly paradoxical findings.

Addiction • October 2014

Just say 'know':

How do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints?

Freeman TP1, Morgan CJ, Hindocha C, Schafer G, Das RK, Curran HV.

Clinical Psychopharmacology Unit, University College London, London, UK

<http://www.ncbi.nlm.nih.gov/pubmed/24894801>

To determine whether measured concentrations of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in individuals' own cannabis predict their estimates of drug potency and actual titration; and (2) to ascertain if these effects are influenced by frequency of use and cannabis type.

When using their own cannabis in a naturalistic setting, people titrate the amount they roll in joints according to concentrations of delta-9-tetrahydrocannabinol (THC) but not cannabidiol (CBD). Recreational users thus show poor understanding of cannabis potency.

Inflammopharmacology • October 2014

Cannabis use by individuals with multiple sclerosis: effects on specific immune parameters

Sexton M1, Cudaback E, Abdullah RA, Finnell J, Mischley LK, Rozga M, Lichtman AH, Stella N.

Center for the Study of Cannabis and Social Policy, Seattle, WA, 98028, USA
msextonn@cannabisandsocialpolicy.org

Full text with 73 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170074/>

Cannabinoids affect immune responses in ways that may be beneficial for autoimmune diseases. We sought to determine whether chronic Cannabis use differentially modulates a select number of immune parameters in healthy controls and individuals with multiple sclerosis (MS cases). Subjects were enrolled and consented to a single blood draw, matched for age and BMI. We measured monocyte migration isolated from each subject, as well as plasma levels of endocannabinoids and cytokines. Cases met definition of MS by international diagnostic criteria. Monocyte cell migration measured in control subjects and individuals with MS was similarly inhibited by a set ratio of phytocannabinoids. The plasma levels of CCL2 and IL17 were reduced in non-naïve cannabis users irrespective of the cohorts. We detected a significant increase in the endocannabinoid arachidonylethanolamine (AEA) in serum from individuals with MS compared to control subjects, and no significant difference in levels of other endocannabinoids and signaling lipids irrespective of Cannabis use. Chronic Cannabis use may affect the immune response to similar extent in individuals with MS and control subjects through the ability of phytocannabinoids to reduce both monocyte migration and cytokine levels in serum. From a panel of signaling lipids, only the levels of AEA are increased in individuals with MS, irrespective of Cannabis use or not. Our results suggest that both MS cases and controls respond similarly to chronic Cannabis use with respect to the immune parameters measured in this study.

Cannabinoids alleviate experimentally induced intestinal inflammation by acting at central and peripheral receptors

Fichna J1, Bawa M2, Thakur GA3, Tichkule R3, Makriyannis A3, McCafferty DM2, Sharkey KA4, Storr M5.

1. Snyder Institute for Chronic Disease, Department of Medicine, University of Calgary, Calgary, Alberta, Canada
Department of Biochemistry, Medical University of Lodz, Lodz, Poland
2. Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada
3. Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts, USA
4. Snyder Institute for Chronic Disease, Department of Medicine, University of Calgary, Calgary, Alberta, Canada
Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada
Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
5. Snyder Institute for Chronic Disease, Department of Medicine, University of Calgary, Calgary, Alberta, Canada
Division of Gastroenterology, Department of Medicine, University of Munich, Munich, Germany

Full text with 48 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4183544/>

In an attempt to further investigate the role of cannabinoid (CB) system in the pathogenesis of inflammatory bowel diseases, we employed two recently developed ligands, AM841 (a covalently acting CB agonist) and CB13 (a peripherally-restricted CB agonist) to establish whether central and peripheral CB sites are involved in the anti-inflammatory action in the intestine.

This is the first evidence that central and peripheral CB receptors are responsible for the protective and therapeutic action of cannabinoids in mouse models of colitis. Our observations provide new insight to CB pharmacology and validate the use of novel ligands AM841 and CB13 as potent tools in CB-related research.

Polski Merkuriusz Lekarski • October 2014

Potential applications of marijuana and cannabinoids in medicine

Zdrojewicz Z, Pypno D, Cabala K, Bugaj B, Waracki M.

<http://www.ncbi.nlm.nih.gov/pubmed/25518584>

Cannabinoids, psychoactive substances present in cannabis, have been known to mankind for hundreds of years. Apart from 9-tetrahydrocannabinol (THC) substances found in the cannabis herb with the highest toxicological value are cannabidiol (CBD) and cannabinol (CBN). The discovery of CB1 and CB2 receptors, located in various tissues (ranging from the brain to peripheral tissues), has defined the potential objective of these new chemical substances' effects. Many studies on the application of cannabinoids in the treatment of various diseases such as diabetes, neoplasms, inflammatory diseases, neurological conditions, pain and vomiting were conducted. Drugs containing e.g. THC appear on the pharmaceutical market. Substances affecting cannabinoid receptors may show beneficial effects, but they may also cause the risk of side effects related mainly to the inhibition of central nervous system. The purpose of this dissertation is the analysis, whether the substances responsible for the effects of marijuana, can find application in medicine. Original articles and reviews were used to summarize the results of studies connected to the topic.

Addiction Behavior • October 2014

A new method of cannabis ingestion: the dangers of dabs?

Loflin M1, Earleywine M2.

<http://www.ncbi.nlm.nih.gov/pubmed/24930049>

A new method for administering cannabinoids, called butane hash oil (“dabs”), is gaining popularity among marijuana users. Despite press reports that suggest that “dabbing” is riskier than smoking flower cannabis, no data address whether dabs users experience more problems from use than those who prefer flower cannabis.

Analyses revealed that using “dabs” created no more problems or accidents than using flower cannabis. Participants did report that “dabs” led to higher tolerance and withdrawal (as defined by the participants), suggesting that the practice might be more likely to lead to symptoms of addiction or dependence.

The use of butane hash oil has spread outside of the medical marijuana community, and users view it as significantly more dangerous than other forms of cannabis use.

Cannabis-associated myocardial infarction in a young man with normal coronary arteries

Hodcroft CJ1, Rossiter MC2, Buch AN3.

1. Department of Acute Medicine, Royal Glamorgan Hospital, Llantrisant, UK
2. Department of Emergency Medicine, University Hospital of Wales, Cardiff, UK
3. East Carolina Heart Institute, East Carolina University, Greenville, North Carolina, USA

<http://www.ncbi.nlm.nih.gov/pubmed/24996293>

The use of cannabis is not usually regarded as a risk factor for acute coronary syndrome. However, several cases of myocardial infarction (MI) associated with cannabis use have been reported in the scientific literature. The etiology of this phenomenon is not known.

We present the case of a previously healthy 21-year-old man who regularly smoked cannabis and presented to the Emergency Department with ST-elevation myocardial infarction after participating in a sport. He was also a cigarette smoker, but had no other conventional cardiovascular risk factors. At coronary angiography, a large amount of thrombus was found in the left anterior descending coronary artery. He recovered with medical treatment, and subsequent intravascular ultrasound examination showed no evidence of atherosclerosis at the site of the thrombus.

Cannabis-associated MI is increasingly recognized. The etiology is unclear, but we believe this is the first report of the phenomenon where atherosclerotic plaque rupture has been excluded as the cause with a high degree of confidence.

Evaluation of Phytocannabinoids from High Potency Cannabis sativa using In Vitro Bioassays to Determine Structure-Activity Relationships for Cannabinoid Receptor 1 and Cannabinoid Receptor 2

Husni AS1, McCurdy CR2, Radwan MM3, Ahmed SA3, Slade D3, Ross SA4, ElSohly MA5, Cutler SJ2.

1. Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677, USA
2. Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677, USA
National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University Mississippi 38677, USA
3. National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University Mississippi 38677, USA
4. National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University Mississippi 38677, USA
Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677, USA
5. National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University Mississippi 38677, USA
Department of Pharmaceutics, School of Pharmacy, University of Mississippi, University, MS 38677, USA

Full text with 25 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4235762/>

Cannabis has been around for thousands of years and has been used recreationally, medicinally, and for fiber. **Over 500 compounds have been isolated from Cannabis sativa with approximately 105 being cannabinoids.**

Of those 105 compounds, Δ^9 -tetrahydrocannabinol has been determined as the primary constituent, which is also responsible for the psychoactivity associated with Cannabis.

Cannabinoid receptors belong to the large superfamily of G protein-coupled receptors. Targeting the cannabinoid receptors has the potential to treat a variety of conditions such as pain, neurodegeneration, appetite, immune function, anxiety, cancer, and others. Developing in vitro bioassays to determine binding and functional activity of compounds has the ability to lead researchers to develop a safe and effective drug that may target the cannabinoid receptors. Using radioligand binding and functional bioassays, a structure-activity relationship for major and minor cannabinoids was developed.

Cannabidiol: promise and pitfalls

Welty TE1, Luebke A2, Gidal BE3.

1. Professor and Chair, Department of Clinical Sciences, College of Pharmacy and Health Sciences, Drake University, Des Moines, IA
2. School of Pharmacy, University of Wisconsin, Madison, WI
3. Professor and Chair, Division of Pharmacy Practice, School of Pharmacy, University of Wisconsin, Madison, WI

Full text with 17 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4189631/>

Over the past few years, increasing public and political pressure has supported legalization of medical marijuana. One of the main thrusts in this effort has related to the treatment of refractory epilepsy—especially in children with Dravet syndrome—using cannabidiol (CBD). Despite initiatives in numerous states to at least legalize possession of CBD oil for treating epilepsy, little published evidence is available to prove or disprove the efficacy and safety of CBD in patients with epilepsy. This review highlights some of the basic science theory behind the use of CBD, summarizes published data on clinical use of CBD for epilepsy, and highlights issues related to the use of currently available CBD products. Cannabidiol is the major nonpsychoactive component of *Cannabis sativa*.

Over the centuries, a number of medicinal preparations derived from *C. sativa* have been employed for a variety of disorders, including gout, rheumatism, malaria, pain, and fever. These preparations were widely employed as analgesics by Western medical practitioners in the 19(th) century (1). More recently, there is clinical evidence suggesting efficacy in HIV-associated neuropathic pain, as well as spasms associated with multiple sclerosis (1).

Young adult sequelae of adolescent cannabis use: an integrative analysis

Silins E1, Horwood LJ2, Patton GC3, Fergusson DM2, Olsson CA4, Hutchinson DM5, Spry E6, Toumbourou JW7, Degenhardt L8, Swift W5, Coffey C6, Tait RJ9, Letcher P10, Copeland J11, Mattick RP5; Cannabis Cohorts Research Consortium.

1. National Drug and Alcohol Research Centre, UNSW Australia, Sydney, NSW, Australia
2. Christchurch Health and Development Study, Department of Psychological Medicine, University of Otago, Christchurch, New Zealand
3. Centre for Adolescent Health, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia
Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia
4. Centre for Adolescent Health, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia
School of Psychology, Deakin University, Geelong, VIC, Australia
Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia
Psychological Sciences, University of Melbourne, Melbourne, VIC, Australia
5. National Drug and Alcohol Research Centre, UNSW Australia, Sydney, NSW, Australia
6. Centre for Adolescent Health, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia
7. Centre for Adolescent Health, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia
School of Psychology, Deakin University, Geelong, VIC, Australia
8. National Drug and Alcohol Research Centre, UNSW Australia, Sydney, NSW, Australia; Centre for Adolescent Health, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia
School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia
Department of Global Health, School of Public Health, University of Washington, Seattle, WA, USA
9. National Drug Research Institute, Faculty of Health Sciences, Curtin University, Perth, WA, Australia
Centre for Research on Ageing Health and Wellbeing, Australian National University, Canberra, ACT, Australia
10. Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia
11. National Cannabis Prevention and Information Centre, UNSW Australia, Sydney, NSW, Australia
Electronic address: e.silins@unsw.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/26360862>

Debate continues about the consequences of adolescent cannabis use. Existing data are limited in statistical power to examine rarer outcomes and less common, heavier patterns of cannabis use than those already investigated; furthermore, evidence has a piecemeal approach to reporting of young adult sequelae. We aimed to provide a broad picture of the psychosocial sequelae of adolescent cannabis use.

We recorded clear and consistent associations and dose-response relations between the frequency of adolescent cannabis use and all adverse young adult outcomes. After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years had clear reductions in the odds of high-school completion (adjusted odds ratio 0.37, 95% CI 0.20-0.66) and degree attainment (0.38, 0.22-0.66), and substantially increased odds of later cannabis dependence (17.95, 9.44-34.12), use of other illicit drugs (7.80, 4.46-13.63), and suicide attempt (6.83, 2.04-22.90).

Adverse sequelae of adolescent cannabis use are wide ranging and extend into young adulthood. Prevention or delay of cannabis use in adolescence is likely to have broad health and social benefits. Efforts to reform cannabis legislation should be carefully assessed to ensure they reduce adolescent cannabis use and prevent potentially adverse developmental effects.

The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study

Eisenberg E, Ogintz M, Almog S.

<http://www.ncbi.nlm.nih.gov/pubmed/25118789>

Chronic neuropathic pain is often refractory to standard pharmacological treatments. Although growing evidence supports the use of inhaled cannabis for neuropathic pain, the lack of standard inhaled dosing plays a major obstacle in cannabis becoming a “main stream” pharmacological treatment for neuropathic pain. The objective of this study was to explore the pharmacokinetics, safety, tolerability, efficacy, and ease of use of a novel portable thermal-metered-dose inhaler (tMDI) for cannabis in a cohort of eight patients suffering from chronic neuropathic pain and on a stable analgesic regimen including medicinal cannabis. In a single-dose, open-label study, patients inhaled a single 15.1 ± 0.1 mg dose of cannabis using the Syqe Inhaler device. Blood samples for $\Delta(9)$ -tetrahydrocannabinol (THC) and 11-hydroxy- $\Delta(9)$ -THC were taken at baseline and up to 120 minutes. Pain intensity (0-10 VAS), adverse events, and satisfaction score were monitored following the inhalation. A uniform pharmacokinetic profile was exhibited across all participants ($\Delta(9)$ -THC plasma $C_{max} \pm SD$ was 38 ± 10 ng/mL, $T_{max} \pm SD$ was 3 ± 1 minutes, $AUC_{0 \text{ TO } \infty} \pm SD$ was 607 ± 200 ng·min/mL). Higher plasma C_{max} increase per mg $\Delta(9)$ -THC administered (12.3 ng/mL/mg THC) and lower interindividual variability of C_{max} (25.3%), compared with reported alternative modes of THC delivery, were measured. A significant 45% reduction in pain intensity was noted 20 minutes post inhalation ($P = .001$), turning back to baseline within 90 minutes. Tolerable, lightheadedness, lasting 15-30 minutes and requiring no intervention, was the only reported adverse event. This trial suggests the potential use of the Syqe Inhaler device as a smokeless delivery system of medicinal cannabis, producing a $\Delta(9)$ -THC pharmacokinetic profile with low interindividual variation of C_{max} , achieving pharmaceutical standards for inhaled drugs.

Journal Of Medical Toxicology • September 2014

Medical Marijuana and Driving: a Review

Mark J. Neavyn, Eike Blohm, Kavita M. Babu, and Steven B. Bird

Department of Emergency Medicine, Division of Medical Toxicology, University of Massachusetts Medical School, 55 Lake Ave North, Worcester, MA 01655 USA
Email: gro.lairomemssamu@nyvaen.kram.

Full text with 70 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4141931/>

Medical marijuana remains a highly debated treatment regimen despite removal of state penalties against care providers prescribing the drug and patients treated with the drug in many areas of the USA. The utility of marijuana in specific medical conditions has been studied at length, but its effects on driving performance and risk of motor vehicle collision remain unclear. As with other medications that affect psychomotor function, the healthcare provider should be informed of the potential risks of driver safety prior to prescribing this psychotropic drug to give appropriate anticipatory guidance for appropriate use. The goal of this narrative review is to assess the current literature regarding marijuana as it relates to driving performance and traffic safety. With a foundation in the pharmacology of cannabinoids, we consider the limitations of testing cannabinoid and metabolite concentration. In addition, we will review studies on driving performance and epidemiological studies implicating marijuana in motor vehicle collisions. The increasing prevalence of medical marijuana laws in the USA suggests that clinicians should be aware of marijuana's influence on public safety. Patients should abstain from driving for 8 h if they achieve a subjective "high" from self-treatment with smoked marijuana and should be aware of the cumulative effects of alcohol and other psychoactive xenobiotics.

Changes in driver cannabinoid prevalence in 12 U.S. states after implementing medical marijuana laws

Masten SV1, Guenzburger GV2.

1,2. California Department of Motor Vehicles, Research and Development Branch, 2570 24th Street, MS H-126, Sacramento, CA 95818-2606, USA
Electronic address: Scott.Masten@dmv.ca.gov

<http://www.ncbi.nlm.nih.gov/pubmed/25142359>

Increased driver cannabinoid prevalence associated with implementing medical marijuana laws was detected in only three states: California, with a 2.1 percentage-point increase in the percentage of all fatal-crash-involved drivers who tested positive for cannabinoids (1.1% pre vs. 3.2% post) and a 5.7 percentage-point increase (1.8% vs. 7.5%) among fatally-injured drivers; Hawaii, with a 6.0 percentage-point increase (2.5 vs. 8.5) for all drivers and a 9.6 percentage-point increase (4.9% vs. 14.4%) among fatally-injured drivers; and Washington, with a 3.4 percentage-point increase (0.7% vs. 4.1%) for all drivers and a 4.6 percentage-point increase (1.1% vs. 5.7%) among fatally-injured drivers. Changes in prevalence were not associated with the ease of marijuana access afforded by the laws.

Increased prevalence of cannabinoids among drivers involved in fatal crashes was only detected in a minority of the states that implemented medical marijuana laws. The observed increases were one-time changes in the prevalence levels, rather than upward trends, suggesting that these laws may indeed provide marijuana access to a stable population of patients as intended, without increasing the numbers of new users over time. Although this study provides some insight into the potential impact of these laws on public safety, differences between states in drug testing practices and regularity, along with the fairly recent implementation of most medical marijuana laws, suggest that the long-term impact of these laws may not yet be known.

Neuromolecular Medicine • September 2014

Functions of the CB1 and CB 2 receptors in neuroprotection at the level of the blood-brain barrier

Vendel E1, de Lange EC.

Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Einsteinweg 55, 2333CC, PO Box 9502, 2300 RA, Leiden, The Netherlands

<http://www.ncbi.nlm.nih.gov/pubmed/24929655>

The cannabinoid (CB) receptors are the main targets of the cannabinoids, which include plant cannabinoids, endocannabinoids and synthetic cannabinoids. Over the last few years, accumulated evidence has suggested a role of the CB receptors in neuroprotection. The blood-brain barrier (BBB) is an important brain structure that is essential for neuroprotection. A link between the CB receptors and the BBB is thus likely, but this possible connection has only recently gained attention. Cannabinoids and the BBB share the same mechanisms of neuroprotection and both protect against excitotoxicity (CB1), cell death (CB1), inflammation (CB2) and oxidative stress (possibly CB independent)-all processes that also damage the BBB. Several examples of CB-mediated protection of the BBB have been found, such as inhibition of leukocyte influx and induction of amyloid beta efflux across the BBB. Moreover, the CB receptors were shown to improve BBB integrity, particularly by restoring the tightness of the tight junctions. This review demonstrated that both CB receptors are able to restore the BBB and neuroprotection, but much uncertainty about the underlying signaling cascades still exists and further investigation is needed.

Oncotarget • August 2014

Cannabinoids as therapeutic agents in cancer: current status and future implications

Chakravarti B1, Ravi J2, Ganju RK3.

1. Division of Endocrinology, Central Drug Research Institute, Lucknow, UP, India

2,3. Department of Pathology, The Ohio State University, Columbus, Ohio, USA

The authors contributed equally to this work

Full text with 183 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171598/>

The pharmacological importance of cannabinoids has been in study for several years. Cannabinoids comprise of (a) the active compounds of the Cannabis sativa plant, (b) endogenous as well as (c) synthetic cannabinoids. Though cannabinoids are clinically used for anti-palliative effects, recent studies open a promising possibility as anti-cancer agents. They have been shown to possess anti-proliferative and anti-angiogenic effects in vitro as well as in vivo in different cancer models. Cannabinoids regulate key cell signaling pathways that are involved in cell survival, invasion, angiogenesis, metastasis, etc. There is more focus on CB1 and CB2, the two cannabinoid receptors which are activated by most of the cannabinoids. In this review article, we will focus on a broad range of cannabinoids, their receptor dependent and receptor independent functional roles against various cancer types with respect to growth, metastasis, energy metabolism, immune environment, stemness and future perspectives in exploring new possible therapeutic opportunities.

Youth marijuana use: state of the science for the practicing clinician

Hadland SE1, Harris SK.

Full text with 67 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4138809/>

Despite widespread marijuana use among adolescents, accurate information on known health effects is poorly disseminated to clinicians and their patients. Amidst rapidly evolving drug policy in the United States and elsewhere, it is imperative that providers understand the short-term and long-term consequences of marijuana use.

Research on regular marijuana use highlights a unique susceptibility of the developing adolescent brain to adverse neurocognitive and psychiatric outcomes. Although studies have not firmly established causality, onset of regular marijuana use in adolescence is associated with later decline in cognitive function, as well as with adult onset of psychosis and anxiety. Educational and employment outcomes may be poorer among regular marijuana-using adolescents. A number of other adverse respiratory, cardiovascular, endocrine and gastrointestinal associations with regular marijuana use have also been established. Good screening tools and promising brief intervention and behavioral treatment programs are available to clinicians, who are in a position to identify problematic marijuana use among adolescents.

A common misperception among youth is that marijuana use is without harm. However, adolescent marijuana use may have measurable, durable, and potentially irreversible effects on later cognitive function and mental health.

Marijuana Use Patterns Among Patients with Inflammatory Bowel Disease

Jessica Ravikoff Allegretti, MD,* Andrew Courtwright, MD, PhD,† Matthew Lucci, BS,* Joshua R. Korzenik, MD,* and Jonathan Levine, MD*

*Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

†Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

Electronic Address: jravikoff@partners.org

Full text with 17 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4126607/>

The prevalence and perceived effectiveness of marijuana use has not been well studied in inflammatory bowel disease (IBD) despite increasing legal permission for its use in Crohn's disease. Health care providers have little guidance about the IBD symptoms that may improve with marijuana use. The aim of this study was to assess the prevalence, sociodemographic characteristics, and perceived benefits of marijuana use among patients with IBD.

A total of 292 patients completed the survey (response rate = 94%); 12.3% of patients were active marijuana users, 39.0% were past users, and 48.6% were never users. Among current and past users, 16.4% of patients used marijuana for disease symptoms, the majority of whom felt that marijuana was "very helpful" for relief of abdominal pain, nausea, and diarrhea. On multivariate analysis, age and chronic abdominal pain were associated with current marijuana use (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.89–0.97; $P < 0.001$ and OR, 3.5; 95% CI, 1.24–9.82; $P = 0.02$). Age and chronic abdominal pain were also multivariate predictors of medicinal use of marijuana (OR, 0.93; 95% CI, 0.89–0.97; $P < 0.001$ and OR, 4.7; 95% CI, 1.8–12.2; $P = 0.001$). Half of the never users expressed an interest in using marijuana for abdominal pain, were it legally available.

A significant number of patients with IBD currently use marijuana. Most patients find it very helpful for symptom control, including patients with ulcerative colitis, who are currently excluded from medical marijuana laws. Clinical trials are needed to determine marijuana's potential as an IBD therapy and to guide prescribing decisions.

The New England Journal Of Medicine • July 2014

Big Marijuana — Lessons from Big Tobacco

Kimber P. Richter, Ph.D., M.P.H., and Sharon Levy, M.D., M.P.H.

The tobacco industry has unfortunately provided a detailed road map for marijuana: deny addiction potential, downplay adverse health effects, create as large a market as possible, and protect it through lobbying, campaign contributions, and other advocacy efforts.

Disclosure forms provided by the authors
are available with the full text of this article at NEJM.org
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SOURCE INFORMATION

From the Department of Preventive Medicine and Public Health, University of Kansas Medical Center, and the University of Kansas Cancer Center — both in Kansas City (K.P.R.); and the Division of Developmental Medicine and Adolescent Substance Abuse Program, Boston Children's Hospital, and Harvard Medical School — both in Boston.

<http://www.nejm.org/doi/full/10.1056/NEJMp1406074>



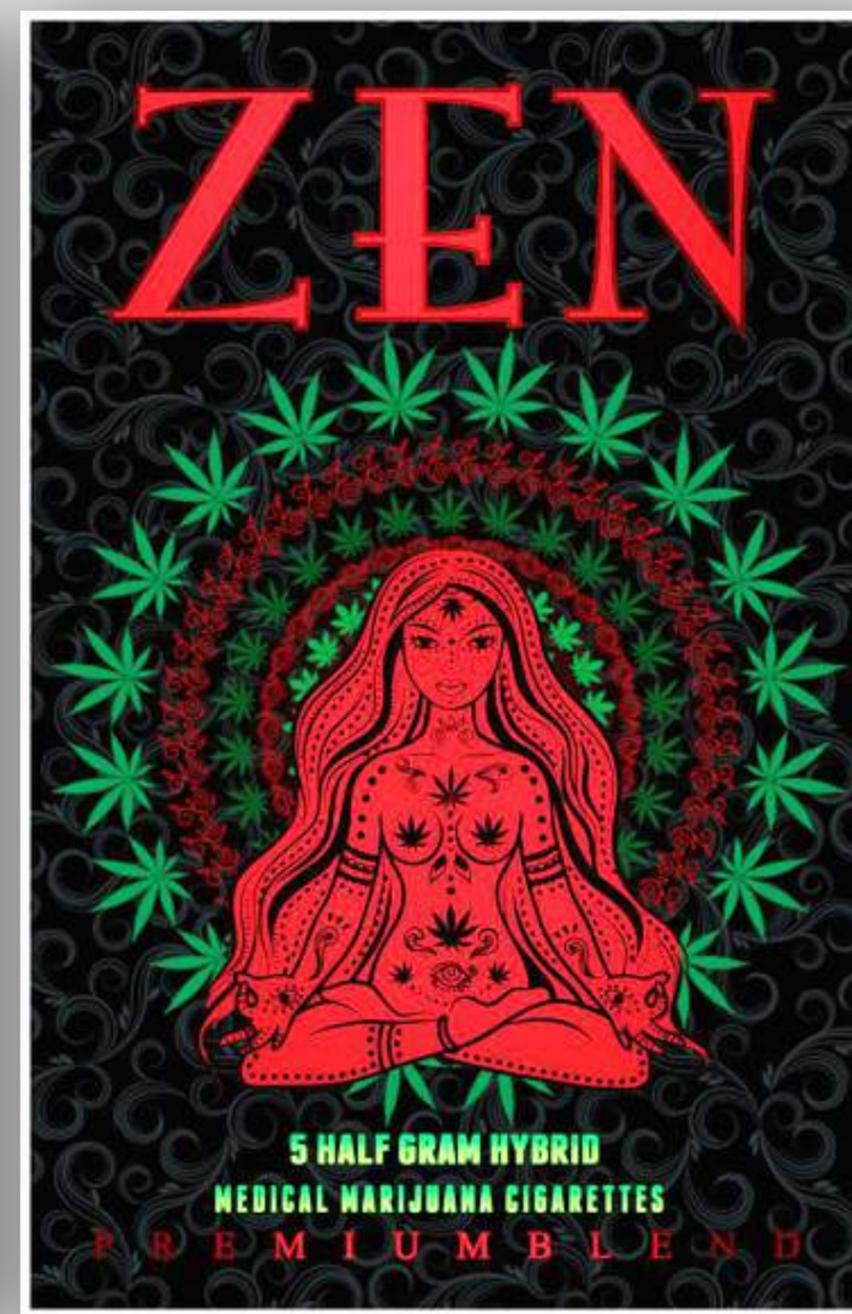
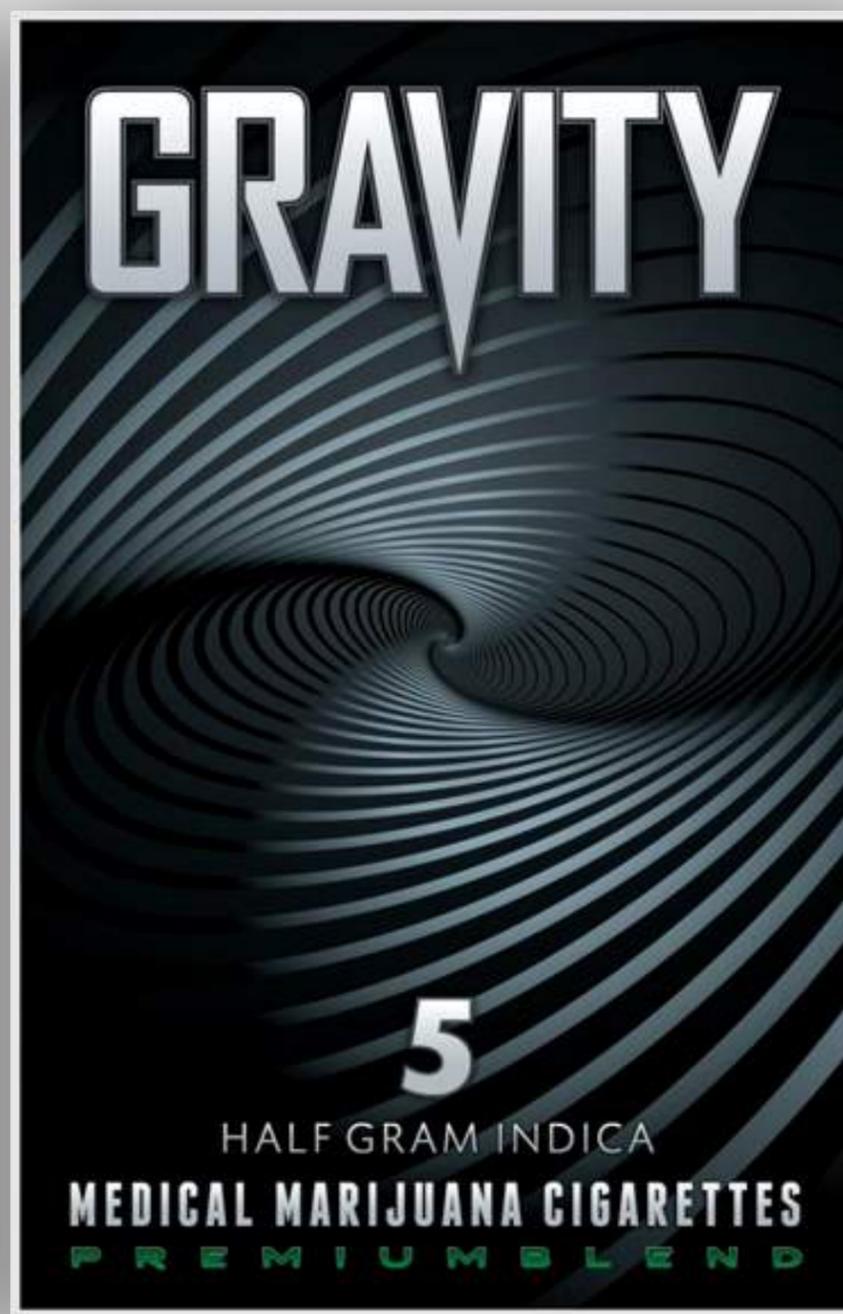
BIG TOBACCO

The term 'Big Tobacco' is a pejorative term most often applied to the tobacco industry in general but more specifically, to the "big three" tobacco corporations in the United States—Philip Morris USA (Altria), R.J. Reynolds (Reynolds American) and Lorillard—merchants of death one and all and the makers of almost every single brand of cigarettes sold at your local bullet proofed corner inconvenience store.

Tobacco is an agricultural product similar in economic terms to gold, silver, pork belly's, corn and other traded commodities. Yet it's also similar to agricultural foodstuffs because the price is determined by total yearly yield which is weather dependent and unpredictable. The price also varies by specific species and cultivars, the amount of product finished and ready to be sold, the location the tobacco was grown (generally the country or region), the health of the crop and a variety of product quality characteristics that can vary from species to species and can also be species specific. Six trillion cigarettes are sold each year with a potential after-tax profit of 600 billion dollars by conservative estimates, perhaps substantially more when one considers Big Tobacco floods the underground illegal markets in countries where cigarettes are banned. It's called "Big" for a reason and it's not the size of the cigarettes. Rest assured, Big Tobacco will put all of the current, smaller, legal purveyors of cannabis in Washington and Colorado and anywhere else they pop up, out of business swiftly—when the time comes, they'll be gone. Big Tobacco is simply waiting for the federal legal issue to be dropped and eventually it will be, and they'll be all in with packs of 20 cannabis cigarettes of every blend and flavor known and new ones we've never heard of, sativa and indica alike. Don't expect Big Tobacco to be hanging back on this one, their strategy is in place and has been for years.

Once the federal laws are changed Big Tobacco will render the packages on the following pages relics and they'll become collectors items.





CALIFORNIA
Finest

100% ORGANIC
HIGH GRADE

SOUR
DIESEL
SATIVA

MARIJUANA CIGARETTES
5 COUNT - 3.5g NET WEIGHT

CALIFORNIA
Finest

HIGH GRADE
LOUD PACK

Cookies
ORIGINAL THIN MINT

MARIJUANA CIGARETTES
5 COUNT - 3.5g NET WEIGHT

CALIFORNIA
Finest

HIGH GRADE
CBD

Charlotte's Web

MARIJUANA CIGARETTES
5 COUNT - 3.5g NET WEIGHT

CALIFORNIA
Finest

100% ORGANIC
HIGH GRADE

GRAND DADDY PURPLE
INDICA
MARIJUANA CIGARETTES

5 COUNT - 3.5g NET WEIGHT

The pack features a black background with a red Golden Gate Bridge and green marijuana leaves at the top. A central green seal with a serrated edge contains a photo of a cannabis bud. Below the seal is a purple banner with the strain name and 'INDICA' in yellow. The bottom text is in yellow and white.

CALIFORNIA
Finest

HIGH GRADE
HYBRID

SOUR
COOKIES
KUSH
MARIJUANA CIGARETTES

5 COUNT - 3.5g NET WEIGHT

The pack has a green and yellow background with a red Golden Gate Bridge and green marijuana leaves at the top. A central yellow seal with a serrated edge contains a photo of a cannabis bud. The strain name is in pink and green bubble letters. The bottom text is in green and white.

CALIFORNIA
Finest

HIGH GRADE
HYBRID

shine®
HAND ROLLED IN 24K GOLD
MARIJUANA CIGARETTES

5 COUNT - 3.5g NET WEIGHT

The pack is primarily black with gold accents, including a red Golden Gate Bridge and gold marijuana leaves at the top. A central black seal with a serrated edge contains a photo of a cannabis bud. The brand name 'shine' is in large gold letters. The bottom text is in gold and white.



CALIFORNIA
Finest

100% ORGANIC
HYDROPONIC

LOG CABIN
PREMIUM
MARIJUANA

CALIFORNIA

PREMIUM

Low
DIESEL

GROWERS RESERVE

10 HALF GRAM
MARIJUANA JOINTS

CALIFORNIA
Finest

100% ORGANIC
HYDROPONIC

BLUE DREAM
PREMIUM MARIJUANA

No. 420



Marijuana

PRE-ROLLED MARIJUANA JOINTS

Current Pharmaceutical Design • July 2014

Effects of cannabis on impulsivity: a systematic review of neuroimaging findings

Wrege J, Schmidt A, Walter A, Smieskova R, Bendfeldt K, Radue EW, Lang UE, Borgwardt S1.

Department of Psychiatry UPK, University of Basel, Petersgraben 4, 4031 Basel, Switzerland
Stefan.Borgwardt@uhbs.ch

Full text with 111 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052819/>

We conducted a systematic review to assess the evidence for specific effects of cannabis on impulsivity, disinhibition and motor control. The review had a specific focus on neuroimaging findings associated with acute and chronic use of the drug and covers literature published up until May 2012. Seventeen studies were identified, of which 13 met the inclusion criteria; three studies investigated acute effects of cannabis (1 fMRI, 2 PET), while six studies investigated non-acute functional effects (4 fMRI, 2 PET), and four studies investigated structural alterations. Functional imaging studies of impulsivity suggest that prefrontal blood flow is lower in chronic cannabis users than in controls. Studies of acute administration of THC or marijuana report increased brain metabolism in several brain regions during impulsivity tasks. Structural imaging studies of cannabis users found differences in reduced prefrontal volumes and white matter integrity that might mediate the abnormal impulsivity and mood observed in marijuana users. To address the question whether impulsivity as a trait precedes cannabis consumption or whether cannabis aggravates impulsivity and discontinuation of usage more longitudinal study designs are warranted.

Marijuana and body weight

Sansone RA1, Sansone LA1.

R. Sansone is a professor in the Departments of Psychiatry and Internal Medicine at Wright State University School of Medicine in Dayton, OH, and Director of Psychiatry Education at Kettering Medical Center in Kettering, OH

L. Sansone is a civilian family medicine physician and Medical Director of the Family Health Clinic at Wright-Patterson Air Force Base Medical Center in WPAFB, OH.

The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or United States Government

Full text with 30 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4204468/>

Acute marijuana use is classically associated with snacking behavior (colloquially referred to as “the munchies”). In support of these acute appetite-enhancing effects, several authorities report that marijuana may increase body mass index in patients suffering from human immunodeficiency virus and cancer. However, for these medical conditions, while appetite may be stimulated, some studies indicate that weight gain is not always clinically meaningful. In addition, in a study of cancer patients in which weight gain did occur, it was less than the comparator drug (megestrol). However, data generally suggest that acute marijuana use stimulates appetite, and that marijuana use may stimulate appetite in low-weight individuals. As for large epidemiological studies in the general population, findings consistently indicate that users of marijuana tend to have lower body mass indices than nonusers. While paradoxical and somewhat perplexing, these findings may be explained by various study confounds, such as potential differences between acute versus chronic marijuana use; the tendency for marijuana use to be associated with other types of drug use; and/or the possible competition between food and drugs for the same reward sites in the brain. Likewise, perhaps the effects of marijuana are a function of initial weight status-i.e., maybe marijuana is a metabolic regulatory substance that increases body weight in low-weight individuals but not in normal-weight or overweight individuals. Only further research will clarify the complex relationships between marijuana and body weight.

Hempseed oil induces reactive oxygen species- and C/EBP homologous protein-mediated apoptosis in MH7A human rheumatoid arthritis fibroblast-like synovial cells

Jeong M1, Cho J1, Shin J1, Jeon YJ1, Kim JH1, Lee SJ2, Kim ES3, Lee K4.

1. Department of Biological Sciences, Konkuk University, 1 Hwayang-dong, Kwangjin-gu, Seoul 143-701, Republic of Korea
2. Department of Biotechnology, Graduate School of Life Sciences & Biotechnology, Korea University, Seoul 136-713, Republic of Korea
3. Department of Biological Sciences, Konkuk University, 1 Hwayang-dong, Kwangjin-gu, Seoul 143-701, Republic of Korea
Korea Hemp Institute, Konkuk University, 1 Hwayang-dong, Kwangjin-gu, Seoul 143-701, Republic of Korea
4. Department of Biological Sciences, Konkuk University, 1 Hwayang-dong, Kwangjin-gu, Seoul 143-701, Republic of Korea
Korea Hemp Institute, Konkuk University, 1 Hwayang-dong, Kwangjin-gu, Seoul 143-701, Republic of Korea
Electronic address: kyungho@konkuk.ac.kr

<http://www.ncbi.nlm.nih.gov/pubmed/24814038>

The medicinal efficacy of hempseed (*Cannabis sativa* L.), which is rich in polyunsaturated fatty acids, in atopic dermatitis, inflammation, and rheumatoid arthritis (RA) has been suggested for centuries. Hempseed has been used as a treatment for these diseases in Korean and Chinese folk medicine. The aim of the study is to investigate the effects of hempseed oil (HO) on MH7A human RA fibroblast-like synovial cells.

Our results suggest that HO treatment induced lipid accumulation, ROS production, CHOP expression, and apoptosis in MH7A cells, and that CHOP functions as an anti-rheumatoid factor downstream of HO in MH7A cells.

Respirology • July 2014

Increasing cannabis use: what we still need to know about its effects on the lung

By D.P. Tashkin

Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, UCLA, Los Angeles, California, USA

Full text, PDF, with 19 references

<http://onlinelibrary.wiley.com/doi/10.1111/resp.12308/epdf>

Lijecnicki Vjesnik • July 2014

Marijuana for medical purposes—public health perspective

By D. Gazdek

<http://www.ncbi.nlm.nih.gov/pubmed/25327006>

Studies show significant negative effects of smoking marijuana on physical and mental health as well as social and occupational functioning. At the same time, there are more considerations about its ability to treat a number of diseases. This review summarizes current data in scientific literature that examines the medical effects of marijuana on human health with particular emphasis on its potential in medicine. Marijuana has a range of adverse health effects, particularly relating to young people because of higher risk for psychosis, traffic accidents, and cognitive impairment. Marijuana may be helpful in relieving symptoms of nausea and vomiting, increasing appetite and pain relief for persons with cancer, AIDS and multiple sclerosis. Smoking marijuana can impose significant public health risks. If there is a medical role for using marijuana, it lies in the application of clearly defined medical protocols and chemically defined compounds, not with using the unprocessed cannabis plant.

Respirology • July 2014

Cannabis smoking and respiratory health: consideration of the literature

Gates P1, Jaffe A, Copeland J.

National Cannabis Prevention and Information Centre, University of New South Wales Medicine, Sydney, New South Wales, Australia

Full text, PDF, with 157 references

<http://onlinelibrary.wiley.com/doi/10.1111/resp.12298/epdf>

The respiratory health effects from tobacco smoking are well described. Cannabis smoke contains a similar profile of carcinogenic chemicals as tobacco smoke but is inhaled more deeply. Although cannabis smoke is known to contain similar harmful and carcinogenic substances to tobacco smoke, relatively little is understood regarding the respiratory health effects from cannabis smoking. There is a need to integrate research on cannabis and respiratory health effects so that gaps in the literature can be identified and the more consistent findings can be consolidated with the purpose of educating smokers and health service providers. This review focuses on several aspects of respiratory health and cannabis use (as well as concurrent cannabis and tobacco use) and provides an update to (i) the pathophysiology; (ii) general respiratory health including symptoms of chronic bronchitis; and (iii) lung cancer.

Fatal crashes from drivers testing positive for drugs in the U.S., 1993-2010

Wilson FA1, Stimpson JP1, Pagán JA2.

1. University of Nebraska Medical Center, Department of Health Services Research and Administration, Omaha, NE
2. New York Academy of Medicine, Center for Health Innovation, New York, NY

Full text with 43 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4037460/>

Illegal drug use is a persistent problem, prescription drug abuse is on the rise, and there is clinical evidence that drug use reduces driving performance. This study describes trends in characteristics of drivers involved in fatal motor vehicle crashes who test positive for drugs.

We used the Fatality Analysis Reporting System—a census of motor vehicle crashes resulting in at least one fatality on U.S. public roads—to investigate suspected drug use for the period 1993-2010.

Drugged drivers who were tested for drug use accounted for 11.4% of all drivers involved in fatal motor vehicle crashes in 2010. Drugged drivers are increasingly likely to be older drivers, and the percentage using multiple drugs increased from 32.6% in 1993 to 45.8% in 2010. About half (52.4%) of all drugged drivers used alcohol, but nearly three-quarters of drivers testing positive for cocaine also used alcohol. Prescription drugs accounted for the highest fraction of drugs used by drugged drivers in fatal crashes in 2010 (46.5%), with much of the increase in prevalence occurring since the mid-2000s.

The profile of a drugged driver has changed substantially over time. An increasing share of these drivers is now testing positive for prescription drugs, cannabis, and multiple drugs. These findings have implications for developing interventions to address the changing nature of drug use among drivers in the U.S.

Marijuana Liberalizations Policies: Why We Can't Learn Much from Policy Still in Motion

By Rosalie Liccardo Pacula and Eric L. Sevigny

R. Pacula is Senior Economist at RAND Corporation, 1776 Main St., P.O. Box 2138, Santa Monica, CA
ERIC L. SEVIGNY is Assistant Professor at University of South Carolina, Currell College, 105 Greene Street, Columbia, SC

Full text with 48 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4051884/>

California legalized the use of marijuana for medicinal purposes nearly 17 years ago, representing a major challenge to the federal government's scheduling of marijuana as a Schedule I drug in the 1970 Controlled Substance Act. As many predicted, California was simply the first. As of May 2013, 19 states and the District of Columbia now provide legal protection to patients, and in many cases caregivers, for possession and supply of marijuana for medicinal purposes. In November 2012, Colorado and Washington went even further legalizing the sale and possession of marijuana for recreational purposes. Given the tremendous natural experiment that is taking place, one might expect that much would already be known about the benefits and harms of liberalizing marijuana policies. Unfortunately, however, the tremendous uncertainty regarding what protections actually exist, and for whom, in addition to the enormous heterogeneity in the medical marijuana laws that continue to change over time, has meant that we do not yet know as much as we should.

The questions of whether marijuana is medicine and whether recreational marijuana use is harmless are necessarily intertwined in all of the debates over policy reform, but these are not the focus of this discussion. There is legitimate evidence that active cannabinoids available in the marijuana plant are useful in the treatment of some medical conditions and symptoms (Leung, 2011; Watson, Benson, & Joy, 2000; Institute of Medicine, 1999) and has been for centuries (Eddy, 2010; Grinspoon, 2005). As such, it is not surprising that the American Medical Association (AMA) adopted a resolution in 2009 urging the federal government to review the case for rescheduling marijuana, noting that doing so would facilitate research and development of cannabinoid-based medicine and avoid the patchwork of inadequate state laws that do not focus on establishing clinical guidelines or standards for medically prescribing marijuana (AMA, 2009). There is also evidence in the biomedical and public health literatures of reasonable pathways through which marijuana can harm health or impact health outcomes (see Hall & Pacula, 2003; Hall & Degenhardt, 2009; Room et al., 2010; or Caulkins et al., 2012 for extensive reviews). However, the causal linkage between recreational marijuana use and many of these health outcomes has yet to be fully established and continues to be a matter of scientific inquiry due to imprecise information on amounts consumed or potency of the substance used. Nonetheless, state liberalization policies move forward, and scientists are trying to use these natural experiments to assist in the identification of benefits and harms from these policies.

Cannabis smoking and lung cancer

Underner M1, Urban T2, Perriot J3, de Chazeron I4, Meurice JC5.

1. Service de pneumologie, unité de tabacologie, CHU La Milétrie, pavillon René-Beauchant, BP 577, 86021 Poitiers, France
Electronic address: m.underner@chu-poitiers.fr
2. Service de pneumologie, CHU d'Angers, 49000 Angers, France
3. Dispensaire Emile-Roux, CLAT 63, 63000 Clermont-Ferrand, France
4. Service de psychiatrie-addictologie, CHU de Clermont-Ferrand, 63000 Clermont-Ferrand, France
5. Service de pneumologie, unité de tabacologie, CHU La Milétrie, pavillon René-Beauchant, BP 577, 86021 Poitiers, France

<http://www.ncbi.nlm.nih.gov/pubmed/25012035>

Cannabis is the most commonly smoked illicit substance in the world. It can be smoked alone in plant form (marijuana) but it is mainly smoked mixed with tobacco. The combined smoking of cannabis and tobacco is a common-place phenomenon in our society. However, its use is responsible for severe pulmonary consequences. The specific impact of smoking cannabis is difficult to assess precisely and to distinguish from the effect of tobacco. Marijuana smoke contains polycyclic aromatic hydrocarbons and carcinogens at higher concentration than tobacco smoke. Cellular, tissue, animal and human studies, and also epidemiological studies, show that marijuana smoke is a risk factor for lung cancer. Cannabis exposure doubles the risk of developing lung cancer. This should encourage clinicians to identify cannabis use and to offer patients support in quitting.

Epilepsia • June 2014

The case for assessing cannabidiol in epilepsy

Cilio MR1, Thiele EA, Devinsky O.

Departments of Neurology and Pediatrics, University of California San Francisco, San Francisco, California, USA

Full text, PDF, with 28 references

<http://onlinelibrary.wiley.com/doi/10.1111/epi.12635/epdf>

Intractable epilepsies have an extraordinary impact on cognitive and behavioral function and quality of life, and the treatment of seizures represents a challenge and a unique opportunity. Over the past few years, considerable attention has focused on cannabidiol (CBD), the major nonpsychotropic compound of *Cannabis sativa*. Basic research studies have provided strong evidence for safety and anticonvulsant properties of CBD. However, the lack of pure, pharmacologically active compounds and legal restrictions have prevented clinical research and confined data on efficacy and safety to anecdotal reports. Pure CBD appears to be an ideal candidate among phytocannabinoids as a therapy for treatment-resistant epilepsy. A first step in this direction is to systematically investigate the safety, pharmacokinetics, and interactions of CBD with other antiepileptic drugs and obtain an initial signal regarding efficacy at different dosages. These data can then be used to plan double-blinded placebo-controlled efficacy trials. A PowerPoint slide summarizing this article is available for download in the Supporting Information section here.

Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders

Devinsky O1, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, Katz R, Di Marzo V, Jutras-Aswad D, Notcutt WG, Martinez-Orgado J, Robson PJ, Rohrback BG, Thiele E, Whalley B, Friedman D.

Department of Neurology, Comprehensive Epilepsy Center, New York University School of Medicine, New York, New York, USA

Full text with 75 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707667/>

To present a summary of current scientific evidence about the cannabinoid, cannabidiol (CBD) with regard to its relevance to epilepsy and other selected neuropsychiatric disorders. We summarize the presentations from a conference in which invited participants reviewed relevant aspects of the physiology, mechanisms of action, pharmacology, and data from studies with animal models and human subjects. Cannabis has been used to treat disease since ancient times. $\Delta(9)$ -Tetrahydrocannabinol ($\Delta(9)$ -THC) is the major psychoactive ingredient and CBD is the major nonpsychoactive ingredient in cannabis. Cannabis and $\Delta(9)$ -THC are anticonvulsant in most animal models but can be proconvulsant in some healthy animals. The psychotropic effects of $\Delta(9)$ -THC limit tolerability. CBD is anticonvulsant in many acute animal models, but there are limited data in chronic models. The antiepileptic mechanisms of CBD are not known, but may include effects on the equilibrative nucleoside transporter; the orphan G-protein-coupled receptor GPR55; the transient receptor potential of vanilloid type-1 channel; the 5-HT_{1a} receptor; and the α_3 and α_1 glycine receptors. CBD has neuroprotective and antiinflammatory effects, and it appears to be well tolerated in humans, but small and methodologically limited studies of CBD in human epilepsy have been inconclusive. More recent anecdotal reports of high-ratio CBD: $\Delta(9)$ -THC medical marijuana have claimed efficacy, but studies were not controlled. CBD bears investigation in epilepsy and other neuropsychiatric disorders, including anxiety, schizophrenia, addiction, and neonatal hypoxic-ischemic encephalopathy. However, we lack data from well-powered double-blind randomized, controlled studies on the efficacy of pure CBD for any disorder. Initial dose-tolerability and double-blind randomized, controlled studies focusing on target intractable epilepsy populations such as patients with Dravet and Lennox-Gastaut syndromes are being planned. Trials in other treatment-resistant epilepsies may also be warranted. A PowerPoint slide summarizing this article is available for download in the Supporting Information section here.

The case for medical marijuana in epilepsy

Maa E1, Figi P.

Comprehensive Epilepsy Program Denver Health and Hospitals, Denver, Colorado, USA
Department of Neurology, University of Colorado, Denver, Colorado, USA

Full text with 14 references

<http://onlinelibrary.wiley.com/doi/10.1111/epi.12610/epdf>

Charlotte, a little girl with SCN1A-confirmed Dravet syndrome, was recently featured in a special that aired on CNN. Through exhaustive personal research and assistance from a Colorado-based medical marijuana group (Realm of Caring), Charlotte's mother started adjunctive therapy with a high concentration cannabidiol/ $\Delta(9)$ -tetrahydrocannabinol (CBD:THC) strain of cannabis, now known as Charlotte's Web. This extract, slowly titrated over weeks and given in conjunction with her existing antiepileptic drug regimen, reduced Charlotte's seizure frequency from nearly 50 convulsive seizures per day to now 2-3 nocturnal convulsions per month. This effect has persisted for the last 20 months, and Charlotte has been successfully weaned from her other antiepileptic drugs. We briefly review some of the history, preclinical and clinical data, and controversies surrounding the use of medical marijuana for the treatment of epilepsy, and make a case that the desire to isolate and treat with pharmaceutical grade compounds from cannabis (specifically CBD) may be inferior to therapy with whole plant extracts. Much more needs to be learned about the mechanisms of antiepileptic activity of the phytocannabinoids and other constituents of *Cannabis sativa*.



Journal Of Law And Medicine • June 2014

**Medical use of cannabis in Australia:
“medical necessity” defences under current Australian law and avenues for reform**

By C. Martin

<http://www.ncbi.nlm.nih.gov/pubmed/25087368>

The possession of cannabis is an offence in all Australian jurisdictions. No exception is made for medical use under any of the State and Territory Drug Acts, nor the Commonwealth’s pharmaceutical regulation scheme. Nevertheless, questions remain about the scope for defences argued on the basis of necessitous medical use. More fundamentally the increasingly favourable light in which the medical use of cannabis is growing to be seen by state and national legislatures overseas raises important questions about the need for reform of Australian drug laws. This article explores those questions.

Current Medicinal Chemistry • June 2014

Is the clinical use of cannabis by oncology patients advisable?

Bar-Sela G, Avisar A, Batash R, Schaffer M1.

Division of Oncology, Rambam Health Care Campus, POB 9602, Haifa 31096, Israel
g_barsela@rambam.health.gov.il

<http://www.ncbi.nlm.nih.gov/pubmed/24606496>

The use of the cannabis plant for various medical indications by cancer patients has been rising significantly in the past few years in several European countries, the US and Israel. The increase in use comes from public demand for the most part, and not due to a scientific basis. Cannabis chemistry is complex, and the isolation and extraction of the active ingredient remain difficult. The active agent in cannabis is unique among psychoactive plant materials, as it contains no nitrogen and, thus, is not an alkaloid. Alongside inconclusive evidence of increased risks of lung and head and neck cancers from prolonged smoking of the plant produce, laboratory evidence of the anti-cancer effects of plant components exists, but with no clinical research in this direction. The beneficial effects of treatment with the plant, or treatment with medicine produced from its components, are related to symptoms of the disease: pain, nausea and vomiting, loss of appetite and weight loss. The clinical evidence of the efficacy of cannabis for these indications is only partial. However, recent scientific data from studies with THC and cannabidiol combinations report the first clinical indication of cancer-related pain relief. The difficulties of performing research into products that are not medicinal, such as cannabis, have not allowed a true study of the cannabis plant extract although, from the public point of view, such studies are greatly desirable.

New England Journal Of Medicine • June 2014

Adverse health effects of marijuana use

Volkow ND1, Baler RD, Compton WM, Weiss SR.

From the National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD

Full text with 77 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827335/>

In light of the rapidly shifting landscape regarding the legalization of marijuana for medical and recreational purposes, patients may be more likely to ask physicians about its potential adverse and beneficial effects on health. The popular notion seems to be that marijuana is a harmless pleasure, access to which should not be regulated or considered illegal. Currently, marijuana is the most commonly used “illicit” drug in the United States, with about 12% of people 12 years of age or older reporting use in the past year and particularly high rates of use among young people.¹ The most common route of administration is inhalation. The greenish-gray shredded leaves and flowers of the *Cannabis sativa* plant are smoked (along with stems and seeds) in cigarettes, cigars, pipes, water pipes, or “blunts” (marijuana rolled in the tobacco-leaf wrapper from a cigar). Hashish is a related product created from the resin of marijuana flowers and is usually smoked (by itself or in a mixture with tobacco) but can be ingested orally. Marijuana can also be used to brew tea, and its oil-based extract can be mixed into food products.

**Cannabinoid-free *Cannabis sativa* L. grown in the Po valley:
evaluation of fatty acid profile, antioxidant capacity and metabolic content**

Lesma G1, Consonni R, Gambaro V, Remuzzi C, Roda G, Silvani A, Vece V, Visconti GL.

1. Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi 19, 20133 Milano, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/24934168>

Within a project aimed to reintroduce non-drug hemp cultivars in the Italian Po valley, for fibre but also high added-value nutraceutical production, investigation on locally grown plants has been performed, in order to assess their oil and metabolic content. This study provides useful information regarding three different hemp cultivars, from two sites, in view of their potential industrial application. The oil was characterised by a high unsaturated/saturated fatty acid ratio and by an almost perfect balance of ω -3 and ω -6 fatty acids, as requested for healthy foods. The alcoholic extracts, for which a high content of amino acids and phenolic compounds has been highlighted, could provide dietary supplements to help in preventing oxidative stress. By investigating the Carmagnola cultivar, six known and four new lignanamides have been identified, confirming and assessing the general metabolic pattern in the seeds of these locally grown plants.

Association of unintentional pediatric exposures with decriminalization of marijuana in the United States

Wang GS1, Roosevelt G2, Le Lait MC3, Martinez EM3, Bucher-Bartelson B3, Bronstein AC3, Heard K4.

1. Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO; University of Colorado Anschutz Medical Campus, Aurora, CO
2. Department of Emergency Medicine, Denver Health, Denver, CO
University of Colorado Anschutz Medical Campus, Aurora, CO
3. Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO
4. Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO
University of Colorado Anschutz Medical Campus, Aurora, CO
Electronic address: george.wang@childrenscolorado.org

<http://www.ncbi.nlm.nih.gov/pubmed/24507243>

We compare state trends in unintentional pediatric marijuana exposures, as measured by call volume to US poison centers, by state marijuana legislation status.

A retrospective review of the American Association of Poison Control Centers National Poison Data System was performed from January 1, 2005, to December 31, 2011. States were classified as nonlegal if they have not passed legislation, transitional if they enacted legislation between 2005 and 2011, and decriminalized if laws passed before 2005. Our hypotheses were that decriminalized and transitional states would experience a significant increase in call volume, with more symptomatic exposures and more health care admissions than nonlegal states.

There were 985 unintentional marijuana exposures reported from 2005 through 2011 in children aged 9 years and younger: 496 in nonlegal states, 93 in transitional states, and 396 in decriminalized states. There was a slight male predominance, and the median age ranged from 1.5 to 2.0 years. Clinical effects varied, with neurologic effects the most frequent. More exposures in decriminalized states required health care evaluation and had moderate to major clinical effects and critical care admissions compared with exposures from nonlegal states. The call rate in nonlegal states to poison centers did not change from 2005 to 2011. The call rate in decriminalized states increased by 30.3% calls per year, and transitional states had a trend toward an increase of 11.5% per year.

Although the number of pediatric exposures to marijuana reported to the National Poison Data System was low, the rate of exposure increased from 2005 to 2011 in states that had passed marijuana legislation.

Journal of Health Economics • May 2014

Medical Marijuana Laws and Illegal Marijuana Use

Yu-Wei Luke Chu

Victoria University of Wellington - School of Economics & Finance

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Full text PDF

econ.msu.edu/seminars/docs/draft100112.pdf

More and more states have passed laws that allow individuals to use marijuana for medical purposes. There is an ongoing, heated policy debate over whether these laws have increased marijuana use among non-patients. In this paper, I address that question empirically by studying marijuana possession arrests in cities from 1988 to 2008. I estimate fixed effects models with city-specific time trends that can condition on unobserved heterogeneities across cities in both their levels and trends. I find that these laws increase marijuana arrests among adult males by about 15–20%. These results are further validated by findings from data on treatment admissions to rehabilitation facilities: marijuana treatments among adult males increased by 10–20% after the passage of medical marijuana laws.

Endocrine Related Cancer • May 2014

Repositioning therapy for thyroid cancer: new insights on established medications

Kushchayeva Y1, Jensen K, Burman KD, Vasko V.

Department of Pediatrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814-4712, USA
Division of Endocrinology, Department of Medicine, Washington Hospital Center, 110 Irving Street Northwest, Washington, District of Columbia, USA

Full text, PDF, with 96 references

<http://erc.endocrinology-journals.org/content/21/3/R183.full.pdf>

Repositioning of established non-cancer pharmacotherapeutic agents with well-known activity and side-effect profiles is a promising avenue for the development of new treatment modalities for multiple cancer types. We have analyzed some of the medications with mechanism of action that may have relevance to thyroid cancer (TC). Experimental in vitro and in vivo evidences, as well as results of clinical studies, have indicated that molecular targets for medications currently available for the treatment of mood disorders, sexually transmitted diseases, metabolic disorders, and diabetes may be active and relevant in TC. For instance, the derivatives of cannabis and an anti-diabetic agent, metformin, both are able to inhibit ERK, which is commonly activated in TC cells. We present here several examples of well-known medications that have the potential to become new therapeutics for patients with TC. Repositioning of established medications for the treatment of TC could broaden the scope of current therapeutic strategies. These diverse treatment choices could allow physicians to provide an individualized approach to optimize treatment for patients with TC.

Science • May 2014

Young brains on drugs

By R.L. DuPont and J.A. Lieberman

Robert L. DuPont was the first director of the U.S. National Institute on Drug Abuse (1973-1978) and is president of the Institute for Behavior and Health, Rockville, MD.

Full text, PDF

<http://science.sciencemag.org/content/sci/344/6184/557.full.pdf>

United States are missing an essential piece of information: scientific evidence about the effects of marijuana on the adolescent brain. Much is known about the effects of recreational drugs on the mature adult brain, but there has been no serious investigation of the risks of marijuana use in younger users. In April 2014, a controversial study suggested that “casual” use of marijuana is associated with structural abnormalities in the brains of young people (aged 18 to 25), particularly in regions vital to emotion, motivation, and decision-making. The fact that the findings are preliminary and disputed indicates that rigorous research is needed to inform discussions about the public health benefits and risks of legalized marijuana.

Although marijuana remains illegal for people under the age of 21 in the United States (including in the two states that have legalized it for adults), young people will almost certainly have greater exposure to, and likely more ways to access, the drug (as they already do with alcohol and tobacco), as new initiatives to change marijuana laws in many states come to fruition. Proponents of legalization argue that the medically harmful effects of marijuana are “no worse” than those of alcohol and tobacco. But even if that is true, it does not mean that the risks are the same. Over the decades, the United States has funded research to study the long-term health effects of alcohol and tobacco, but not marijuana. Yet many of the most worrisome brain pathologies from drug use are seen in mental health (as opposed to pulmonary disease and cancer with smoking, and gastric and liver disease with alcohol), where marijuana use is associated with, among other conditions, anxiety and psychotic disorders. Research suggests that early marijuana use is linked to these problems, but their biological under-pinnings are a mystery.

The National Survey on Drug Use and Health has repeatedly found that children who began alcohol or marijuana use before age 15 had a fivefold-increased prevalence of substance use disorders later in life. This may be due to effects of early drug use on the trajectory of the brain's subsequent development, but we don't know for sure. What is needed are large longitudinal cohort studies to examine whether marijuana use causes changes in brain function and behavior in young people. The Framingham Heart Study, still ongoing after its initiation 65 years ago, revolutionized our understanding of what causes cardiovascular disease, producing completely unanticipated findings that have led to improved health care and public policy.

The U.S. National Institutes of Health should launch a similar long-term study of pre-adolescent children and follow them through adolescence into young adulthood, when their brains are most plastic, rapidly developing, reorganizing, and forming enduring neural connections and circuits. The rapid growth of brain science in the past two decades has generated new methods to measure the effects of drugs on brain structure and mental processes. With "big brain" research projects now under way in the United States and Europe, including the BRAIN Initiative announced by President Obama in 2013, to deduce how brain function is linked to behavior and disease, the time is right to rigorously pursue a long-term study of drug effects. Without more scientific evidence to inform policies, we are gambling with the health and safety of our youth in making decisions about psychoactive substances such as marijuana when their real risks are unknown.

The Dilemma of Medical Marijuana Use by Rheumatology Patients

1Dr. Mary-Ann Fitzcharles and 2Dr. Daniel J. Clauw

1. Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada

2. University of Michigan Medical Center, Ann Arbor

E-mail: mary-ann.fitzcharles@muhc.mcgill.ca

Dr. Fitzcharles has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) from Abbott, Amgen, Lilly, Pfizer, Purdue, and Valeant

Dr. Clauw has received consulting fees, speaking fees, and/or honoraria (less than \$10,000 each) and/or research grants from Cerephex, Forest, Johnson & Johnson, Lilly, Merck, Nuvo, Pfizer, Purdue, Theravance, and Tonix

Full text with 37 references

<http://onlinelibrary.wiley.com/doi/10.1002/acr.22267/full>

“Severe pain” is the most common reason for medicinal herbal cannabis use, with arthritis and musculoskeletal pain cited as the most prevalent specific medical condition ([1, 2]). Eighty percent of marijuana users in a US pain clinic report use for myofascial pain, whereas up to one-third of persons in population studies in the UK and Australia reported use for treatment of arthritis pain ([1-3]). Similarly, “severe arthritis” is the diagnosis for 65% of Canadians authorized to possess cannabis for medicinal purposes as of June 2013 ([4]). Medical marijuana has, however, never been recommended by any rheumatology group worldwide for symptom relief in rheumatic conditions. As the health care professionals best placed to advise on issues of rheumatic diseases, rheumatologists must have a voice in the current debate concerning medical marijuana, hereafter identified as herbal cannabis.

Advocacy for access to cannabinoid treatments has led to a societal groundswell, with regulatory bodies around the globe considering the legalization of herbal cannabis for medicinal use. Currently, herbal cannabis is legalized for medicinal use in 20 states in the US as well as in the District of Columbia. Physicians will therefore be caring for patients who may be self-medicating with herbal cannabis or may request medical advice about cannabis. In order to responsibly advise

patients on any medical issue, and in particular herbal cannabis, it is essential that the health care professional has a competent knowledge of the subject based on sound scientific study. In this review, we examined the current evidence for dosing and administration, efficacy, and risks of herbal cannabis in rheumatic pain management, and thereby addressed practical issues confronting rheumatologists whose patients request advice. We confined our comments to herbal cannabis as it pertains to rheumatic conditions, acknowledging that evidence and information may differ for other conditions. We did not enter into the debate addressing the legalization of recreational herbal cannabis.

Herbal cannabis

Prior to present day pharmacology, healers and patients sought relief from pain and suffering by using natural products. The plant *Cannabis sativa*, commonly known as marijuana, has been used for pain relief for millennia, with additional effects on appetite, sleep, and mood, but with psychoactive properties leading to recreational use ([5]). The analgesic effects of herbal cannabis, derived from the dried leaves and flowers, have been most studied in neuropathic pain conditions.

C. sativa contains more than 450 compounds, with at least 70 classified as phytocannabinoids, two of which have particular medical interest ([6]). The acid precursor of Δ 9-tetrahydrocannabinol (Δ 9-THC), transformed by heat into THC, has psychoactive and pain-relieving properties. The second molecule is cannabidiol, with lesser affinity for the cannabinoid receptors and the potential to counteract the negative effects of THC on memory, mood, and cognition. Cannabinoid molecules interact with at least two receptors of the human endocannabinoid system to induce physiologic effects ([7, 8]).

Herbal cannabis may be ingested or inhaled, with the latter route preferred by users due to onset of action within a few minutes. Smoking of cannabis is, however, not medically recommended due to the potential respiratory tract dangers of noxious compounds such as polycyclic aromatic hydrocarbons, tar, and carbon monoxide. Furthermore, plasma concentrations of THC achieved by smoking a "joint," containing between 0.5 and 1.0 gm of dried substance, are extremely variable, with blood levels varying between 7 and 100 ng/ml. Finally, blood levels are influenced by the plant concentration of THC, variable THC delivered in the smoke, and characteristics of the smoking method (frequency of inhalation, hold time, and inhalation volume) ([9, 10]). There is also discordance between the measured THC plasma peak and the maximum subjective psychoactive effects that occur an hour later, and can be augmented by opioids. Oral administration results in a more delayed effect, lower peak plasma levels, more protracted pharmacologic effects, and less abuse-related psychoactive effects ([11]). However, gastrointestinal absorption is more erratic and much of the ingested cannabinoid is eliminated by first-pass metabolism in the liver ([11]).

The mean concentration of THC in illicit marijuana has almost doubled worldwide in the past decade ([12]). With THC content of the plant material varying between 1% and 30%, and the bioavailability varying between 2% and 56%, there is no reasonable method to estimate dosing of the herbal

compound ([13]). Since acquisition of herbal cannabis for medical reasons is mostly via the illegal route, even where medical use is legalized, these higher concentrations of THC might lead to increased physical and psychomotor effects. Therefore, the lack of the most elementary requirements for responsible drug administration must call into question any use of herbal cannabis for rheumatic pain treatment at this time.

As arthritis pain contributes to poor patient global well-being, pain relief is an important outcome goal, but unfortunately, pain treatments remain sub-optimal in most patients ([14]). The overriding principle for any pain treatment is to maintain function without sacrificing cognitive or psychomotor function, a concept clearly different from pain management for medical conditions predominantly requiring palliation.

Chronic rheumatic pain remains a challenge, since pain mechanisms are complex dynamic interactions of molecules and nerve pathways subject to nervous system plasticity. Available drugs generally offer a modest effect only, and pain co-associates with sleep disturbance and mood disorders. As treatment success is considered a 30% reduction in pain, and because most pain-relieving medications are associated with considerable side effects, the compliance with prescribed treatments is often poor. It is therefore understandable that patients will continue to seek other remedies to reduce symptoms. Patients with rheumatic disease commonly use complementary and alternative medicine, and with increasing advocacy for legalization of herbal cannabis as a recreational drug, cannabis may be perceived as a safe treatment option.

To date, there is no formal study examining the efficacy or adverse effects of herbal cannabis in rheumatic diseases ([15]). Since our previous review, there has been only a single additional study reporting poorer function and psychological health in fibromyalgia patients using cannabinoids ([16]). While

there is good evidence for efficacy of cannabinoids for treating some chronic pain conditions, such as cancer and neuropathic pain, these pain types have a different underlying mechanism from the mostly peripheral/nociceptive pain in rheumatic diseases ([17]). Therefore, one cannot extrapolate efficacy to patients with rheumatic conditions.

Information about the effects of cannabinoids in rheumatic diseases is currently derived from anecdotal reports, two small epidemiologic studies, a single study of the oromucosal spray of nabiximols, a combination of Δ^9 -THC and cannabidiol, in patients with rheumatoid arthritis, and two studies of nabilone, a synthetic analog of THC, in fibromyalgia ([1, 2, 18-20]). The two population studies from the UK and Australia, with prevalent use for musculoskeletal symptoms, raise a number of concerns: diagnosis and outcome were by patient self-report, patients self-medicated without knowledge of dosing or concomitant treatments, and one-third of the users reported recreational use ([1, 2]). Conclusions based on these studies are therefore questionable. In contrast, when the nabiximol was examined in a randomized clinical trial of 58 patients with rheumatoid arthritis over a 5-week period, there was improvement in pain and quality of sleep ([20]). The nabilone studies in fibromyalgia patients showed improved pain in one, and noninferiority to amitriptyline for the effect on sleep for the other ([18, 19]). However, the reported effects of these agents, which indeed belong to the class of cannabinoids, cannot necessarily be applied to herbal cannabis, which is a different substance, as described above.

It therefore follows that critical evaluation of safety issues that pertain to both short-term and long-term effects of herbal cannabis also have never been formally reported in persons with classic rheumatic diseases. There is also no sound information regarding the recommended dosing of herbal cannabis, other than patient report. Therefore, the available evidence for efficacy of medical herbal cannabis represents the least convincing form of

scientific evidence. Contrary to public belief, inhaled herbal cannabis is not innocuous. Risks can be categorized as the immediate effects on cognition, psychomotor function, cardiovascular effects, and mood, and the chronic consequences on mental ability, pulmonary function, potential cancer risk, and drug dependence. Information on risks of herbal cannabis is also mostly derived from reports of recreational users, who are usually younger and in better health than those with a chronic disease. Additionally, the interaction of herbal cannabis with other medications that are being used therapeutically is mostly unknown.

Acute risks

The acute dose-related effects on cognition and psychomotor function are the most well-known immediate consequences of herbal cannabis use, with implications for patient safety. Following administration of inhaled cannabis in varying THC concentrations, regular cannabis users showed impairment in reaction time, selective attention, short-term memory, and motor control for up to 5 hours following consumption, with increasing effects for increasing doses ([21]). Similarly, the memory-impairing effects of acute cannabis use, possibly specifically attributable to THC, should be kept in mind. These acute effects have implications for medicinal use for two reasons: THC content in street cannabis is increasing and chronic pain management requires continued treatment.

Adverse acute effects on psychomotor function are particularly relevant when subjects drive motorized vehicles. Arthritis per se is seldom a contraindication to drive, and driving in the developed world is an important contribution to independence and quality of life. Acute cannabis use is increasingly appreciated as an accident risk for drivers. In a systematic review and meta-analysis of 9 studies, with inclusion of 49,000 participants, acute cannabis use was associated with at least twice the risk of serious and fatal

motor vehicle collisions ([22]). Indeed, cannabis was also the most prevailing illicit drug identified in 0.5–7.6% of seriously injured drivers from 6 European countries ([23]). Although alcohol remains the most common substance identified in injured drivers, cannabis was ranked second, with the risk increased when combined with alcohol. Health Canada warns that the ability to drive or perform activities requiring alertness or coordination may be impaired for up to 24 hours following a single consumption ([24]). Therefore, driving with the concomitant use of herbal cannabis is both a personal and a societal safety risk, which may be further compounded in the presence of other medications. At the very least, medical practitioners must now advise patients that herbal cannabis may impair motor coordination, particularly when driving. However, advising patients not to drive is a recommendation counterintuitive to maintaining normal function.

A less appreciated effect of acute cannabis is noted for the cardiovascular system. Tachycardia and hypotension could compromise cardiovascular status in those with underlying heart disease and be a risk for cardiovascular events ([25]). Cannabis increases the risk of myocardial infarction 5-fold and reduces the exercise capacity of those with angina pectoris by half ([26, 27]). Lastly, immediate psychiatric effects are increasingly associated with acute cannabis use, including anxiety, agitation, suicidal ideation, and acute psychosis ([28]).

Chronic risks

The long-term risks of herbal cannabis use in patients with rheumatic disease are unknown. Risks generic to all persons using herbal cannabis include effects on psychological health and association with mental illness, development of dependence and addiction, effects on memory, and cognition and respiratory health ([28]). Aggravation of depression- and smoking-associated risks may be particularly important for rheumatology patients. These issues seem to be particularly problematic in younger individuals, where we

appreciate that many neuroactive drugs may have additional or more pronounced side effects ([29]). For example, just as suicidality with selective serotonin reuptake inhibitors seems more pronounced in individuals ages <25 years, there is a similar age predisposition for the increased risk of psychosis in young cannabis users.

Although the long-term effect on mood and especially depression still remains unclear, depression is more prevalent in current cannabis users ([30]). In a US study of more than 8,000 adults, those with cannabis use in the past year had 1.4 times higher odds of current depression than nonusers ([30]). Aggravation or unmasking of serious psychiatric disease also occurs with herbal cannabis use. Although previously disputed, cannabis is now generally accepted as an agent with addictive potential, especially in a context of an adverse psychosocial setting. Over a 3-year period, the cumulative incidence of cannabis dependence was 37.2% (95% confidence interval [95% CI] 30.7–43.8%) for young recreational users ([31]).

While cigarette smoking–associated risks for arthritis patients cannot immediately be attributed to the smoking of herbal cannabis, the potential for these adverse effects exists. Apart from the consequences of inhalation of an irritant on respiratory mucosa with development of chronic respiratory disease, there is increasing evidence that herbal cannabis may independently increase risk of lung cancer ([32–34]). When Swedish military conscripts ages 18–20 years were tracked over a 40-year period, those who had smoked cannabis on at least 50 occasions had a 2-fold risk (hazard ratio 2.12, 95% CI 1.08–4.14) of developing lung cancer, even after adjustments for other risks for lung cancer ([34]). Although it is recommended that herbal cannabis not be smoked, this remains the most common route of administration for most persons.

Finally, the true motive for use of herbal cannabis, even in persons with an

identifiable medical condition, requires careful scrutiny. Often, persons using marijuana for medical reasons have previously been recreational users, raising the possibility of misusing a medical diagnosis to justify use primarily for nonmedical reasons ([1, 2, 35]).

Understanding the dilemma for the health care professional

Responsible medical practice requires a physician to provide empathetic and judicious patient care without harm. In light of the current lack of concrete medical evidence for either the efficacy or risks of herbal cannabis for the management of rheumatic symptoms, physicians are obligated to caution patients about the known risks of herbal cannabis that have been reported for recreational users. Simply acceding to patient demands for a treatment on the basis of popular advocacy, without comprehensive knowledge of an agent, does not adhere to the ethical standards of medical practice. It is understandable that this lack of current scientific evidence must translate into physician insecurity and even distress when attempting to provide rational advice to a patient. Furthermore, any recommended therapy requires proof of concept by sound scientific study that attests to both efficacy and safety. Therefore, before physicians can provide medical recommendation or support for use of herbal cannabis, the minimal standards for pharmacotherapy must be met. At present, these elementary criteria are not fulfilled. In the absence of knowledge of effective dosing or true benefits for herbal cannabis for rheumatic symptoms, the risks extrapolated from study of persons with recreational use seem to tip the balance against use. Therefore, we believe that herbal cannabis should not at this time be allowed exceptional status as a therapy, different from other modes of therapy.

The question arises, then, whether physicians have any basis on which to provide responsible advice to patients beyond the known risk of serious adverse effects. In many jurisdictions, legislation is forcing physicians to accept

medical responsibility for their patients who may be using herbal cannabis. For example, in Canada, physicians will be required to provide a document equivalent to a prescription stipulating dosing, frequency, and duration of use ([24, 36]). An additional challenge is presented by the ambiguous terminology used by the courts whereby legal access to herbal cannabis is deemed a Charter Right when a “medical need” has been demonstrated by the patient. If physicians are to “prescribe” medical cannabis for their patients, medical ethics and deontology require physician competence with the prescribed treatment. It is also increasingly recognized that sanctioning use of herbal cannabis for therapeutic reasons is currently provided by small numbers of physicians for the majority of patients ([35]). In the state of Colorado, almost half of the recommendations had been made by only 15 physicians. Motives for this medical behavior should be questioned and raise ethical concerns.

It is therefore not surprising that recent surveys report that physicians lack confidence in their knowledge of cannabinoids and in their competence to effectively advise patients on the use of medicinal cannabinoids ([35]). In a survey of family physicians in Colorado, only 19% thought that physicians should recommend medical marijuana, with 92% reporting the need for more education ([35]). Similarly, two-thirds of Canadian rheumatologists recently surveyed expressed poor confidence in their knowledge of cannabinoid medical use, with 70% stating that there is currently no role for herbal cannabis in the treatment of rheumatic symptoms ([37]). Even in the setting of some reasonable knowledge of cannabinoid molecules and the endocannabinoid system, the absence of evidence for clinical use of herbal cannabis in rheumatic conditions must be discomfiting for any health care professional or rheumatologist intending to provide an herbal cannabis treatment recommendation. Additional knowledge of these molecules is required, but knowledge alone will not fill the void due to absence of clinical study. This evident mismatch between dictates from regulatory bodies, patient advo-

cacy, and prudent clinical care is troubling; irresponsible requirements by regulatory authorities might compromise patient and society well-being. In light of other available treatment options for the management of arthritis pain, lack of sound evidence for effect, and potential for harm, herbal cannabis cannot be recommended for arthritis pain management at this time.

Conclusion

There is an ever-increasing hiatus between public advocacy for herbal cannabis as a therapeutic agent in rheumatic conditions and the medical evidence for efficacy and side effects. This serious shortfall covers many aspects of herbal cannabis as a therapeutic agent, including uncertainty of compound content, unknown dosing, recommendations not to use by inhalation, and the indicators of harm, both in the acute as well as chronic setting. Taking all factors into consideration, health care professionals should currently dissuade rheumatology patients from using herbal cannabis as a therapy. The evident mismatch between patients' needs and good medical practice may in part be politically driven, with regulatory bodies acceding to public pressure. Rheumatologists should advocate for further study of individual cannabinoid molecules whereby dosing can be accurately controlled and efficacy and safety can be assessed using a standard scientific method.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Inhibition of colon carcinogenesis by a standardized *Cannabis sativa* extract with high content of cannabidiol

Romano B1, Borrelli F2, Pagano E2, Cascio MG3, Pertwee RG3, Izzo AA4.

1. Department of Pharmacy, University of Naples Federico II, Naples, Italy; Endocannabinoid Research Group, Italy
School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom
2. Department of Pharmacy, University of Naples Federico II, Naples, Italy; Endocannabinoid Research Group, Italy
3. School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom
4. Department of Pharmacy, University of Naples Federico II, Naples, Italy; Endocannabinoid Research Group, Italy
Electronic address: aaizzo@unina.it

<http://www.ncbi.nlm.nih.gov/pubmed/24373545>

Colon cancer is a major public health problem. Cannabis-based medicines are useful adjunctive treatments in cancer patients. Here, we have investigated the effect of a standardized *Cannabis sativa* extract with high content of cannabidiol (CBD), here named CBD BDS, i.e. CBD botanical drug substance, on colorectal cancer cell proliferation and in experimental models of colon cancer in vivo.

CBD BDS and CBD reduced cell proliferation in tumoral, but not in healthy, cells. The effect of CBD BDS was counteracted by selective CB1 and CB2 receptor antagonists. Pure CBD reduced cell proliferation in a CB1-sensitive antagonist manner only. In binding assays, CBD BDS showed greater affinity than pure CBD for both CB1 and CB2 receptors, with pure CBD having very little affinity. In vivo, CBD BDS reduced AOM-induced preneoplastic lesions and polyps as well as tumour growth in the xenograft model of colon cancer.

CBD BDS attenuates colon carcinogenesis and inhibits colorectal cancer cell proliferation via CB1 and CB2 receptor activation. The results may have some clinical relevance for the use of Cannabis-based medicines in cancer patients.

Lung India • April 2014

Medical marijuana: A panacea or scourge

Kashyap S1, Kashyap K2.

1. Department of Pulmonary Medicine, Kalpana Chawla Government Medical College, Karnal, Haryana, India
2. Ex-Intern, Government Medical College and Hospital, Chandigarh, India

Full text with 42 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999675/>

Marijuana (*Cannabis sativa*) has been used for recreational and medical purposes since ages. Marijuana smoking is an evil, which is on the rise with about 180.6 million active users worldwide. The recent legalization of marijuana in Uruguay has generated global interest. The purpose of this short review is to describe the various preparations, uses and adverse effects of medical marijuana. It also deals with the adverse effects of marijuana smoking when used for recreational purposes. Based on the current literature, medical use of marijuana is justified in certain conditions as an alternative therapy.

Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology

Koppel BS1, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D.

From the Department of Neurology (B.S.K.), New York Medical College, New York
the Department of Neurology (J.C.M.B.), Columbia University College of Physicians & Surgeons, New York Neurological Institute, New York
University of Arizona College of Medicine (T.F.), Phoenix; the Department of Neurology (J.B.), David Geffen School of Medicine at University of California Los Angeles, The VA Greater Los Angeles Healthcare System
the Department of Neurology (S.Y.), University of New Mexico Health Sciences Center, Albuquerque; the Department of Neurology (G.G.), University of Kansas School of Medicine, Kansas City
and the Department of Neurology (D.G.), Geisinger Health System, Danville, PA

Full text with 40 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4011465/>

We performed a systematic review of medical marijuana (1948-November 2013) to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders. We graded the studies according to the American Academy of Neurology classification scheme for therapeutic articles. Thirty-four studies met inclusion criteria; 8 were rated as Class I.

The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy.

The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications.

Cannabinoid control of brain bioenergetics: Exploring the subcellular localization of the CB1 receptor

Hebert-Chatelain E1, Reguero L2, Puente N2, Lutz B3, Chaouloff F1, Rossignol R4, Piazza PV1, Benard G1, Grandes P2, Marsicano G1.

1. INSERM U862, NeuroCentre Magendie, 33077 Bordeaux, France; University of Bordeaux, 33077 Bordeaux, France
2. Department of Neurosciences, Faculty of Medicine and Dentistry, University of the Basque Country UPV/EHU, 48940 Leioa, Spain
3. Institute of Physiological Chemistry, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
4. University of Bordeaux, 33077 Bordeaux, France; Laboratoire Maladies Rares: Génétique et Métabolisme, 33077 Bordeaux, France

<http://www.ncbi.nlm.nih.gov/pubmed/24944910>

Brain mitochondrial activity is centrally involved in the central control of energy balance. When studying mitochondrial functions in the brain, however, discrepant results might be obtained, depending on the experimental approaches. For instance, immunostaining experiments and biochemical isolation of organelles expose investigators to risks of false positive and/or false negative results. As an example, the functional presence of cannabinoid type 1 (CB1) receptors on brain mitochondrial membranes (mtCB1) was recently reported and rapidly challenged, claiming that the original observation was likely due to artifact results. Here, we addressed this issue by directly comparing the procedures used in the two studies. Our results show that the use of appropriate controls and quantifications allows detecting mtCB1 receptor with CB1 receptor antibodies, and that, if mitochondrial fractions are enriched and purified, CB1 receptor agonists reliably decrease respiration in brain mitochondria. These data further underline the importance of adapted experimental procedures to study brain mitochondrial functions.

Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users

Gilman JM¹, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, van der Kouwe A, Blood AJ, Breiter HC.

Laboratory of Neuroimaging and Genetics, Department of Psychiatry, Mood and Motor Control Laboratory
Center for Morphometric Analysis, Department of Psychiatry, and Athinoula A. Martinos Center in Biomedical Imaging
Department of Radiology, Massachusetts General Hospital, Charlestown, Massachusetts, USA
Harvard Medical School, Boston, Massachusetts 02115, and Warren Wright Adolescent Center
Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Full text with 61 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3988409/>

Marijuana is the most commonly used illicit drug in the United States, but little is known about its effects on the human brain, particularly on reward/aversion regions implicated in addiction, such as the nucleus accumbens and amygdala. Animal studies show structural changes in brain regions such as the nucleus accumbens after exposure to Δ^9 -tetrahydrocannabinol, but less is known about cannabis use and brain morphometry in these regions in humans. We collected high-resolution MRI scans on young adult recreational marijuana users and nonusing controls and conducted three independent analyses of morphometry in these structures: (1) gray matter density using voxel-based morphometry, (2) volume (total brain and regional volumes), and (3) shape (surface morphometry). Gray matter density analyses revealed greater gray matter density in marijuana users than in control participants in the left nucleus accumbens extending to subcallosal cortex, hypothalamus, sublenticular extended amygdala, and left amygdala, even after controlling for age, sex, alcohol use, and cigarette smoking. Trend-level effects were observed for a volume increase in the left nucleus accumbens only. Significant shape differences were detected in the left nucleus accumbens and right amygdala. The left nucleus accumbens showed salient exposure-dependent alterations across all three measures and an altered multimodal relationship across measures in the marijuana group. These data suggest that marijuana exposure, even in young recreational users, is associated with exposure-dependent alterations of the neural matrix of core reward structures and is consistent with animal studies of changes in dendritic arborization.

MRI Image On Following Page

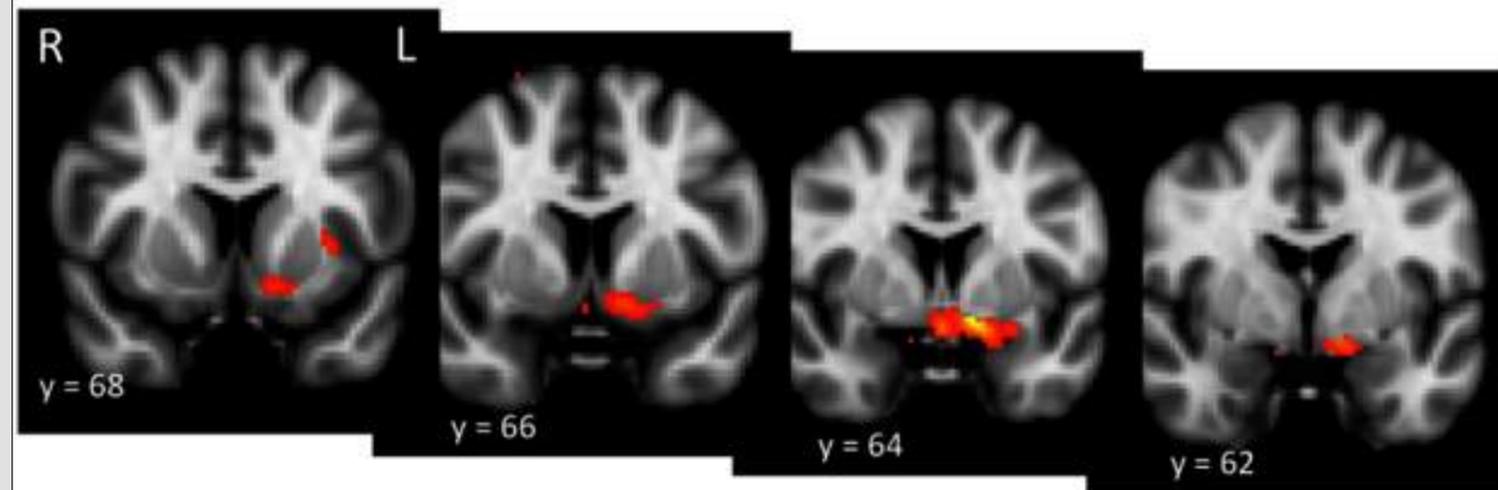
A • Whole-brain voxel-based morphometry between marijuana users and control participants. Images are thresholded at $z = 2.5$.

The most significant increases in gray matter density were in the left nucleus accumbens extending to the hypothalamus, sublenticular extended amygdala, and amygdala (Tables 2 and 3).

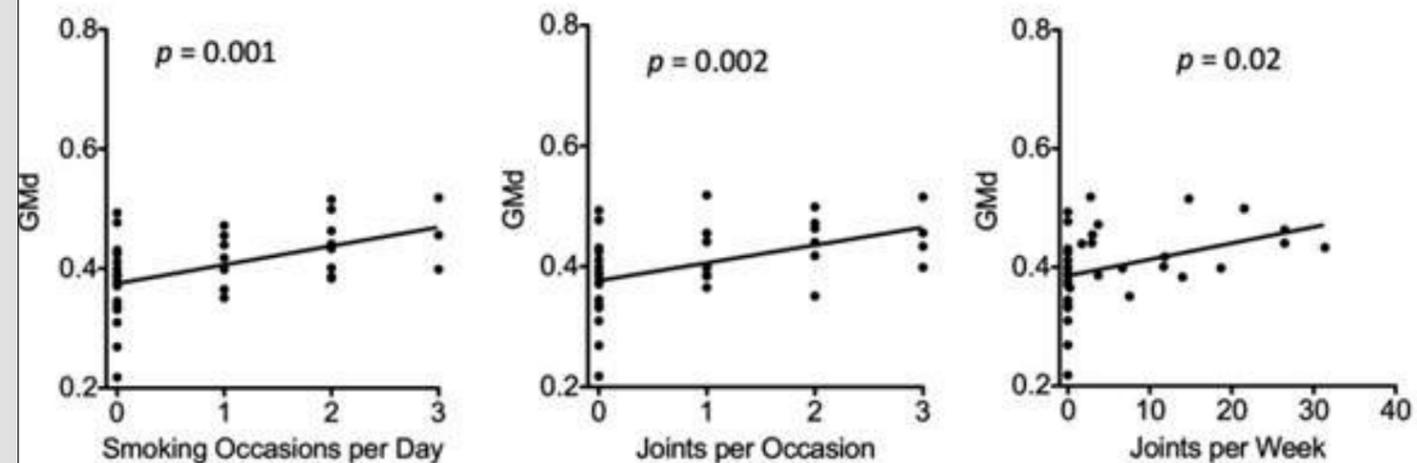
B • Associations between gray matter density and drug use measures; $p < 0.0125$ was considered to be significant after correcting for 4 comparisons (Table 4). GMd, Gray matter density.

C • Nucleus accumbens volume was increased in marijuana users and was associated with drug use measures. Error bars represent SE. An asterisk above the bar chart on left indicates that significance met $p < 0.05$ uncorrected ($p = 0.037$; Table 2), which was a trend effect after correcting multiple comparisons. The association with drug use, after correcting for 4 comparisons ($p = 0.05/4$, or 0.0125), was determined to be a trend toward significance (Table 4). CON, Controls; MJ, marijuana participants.

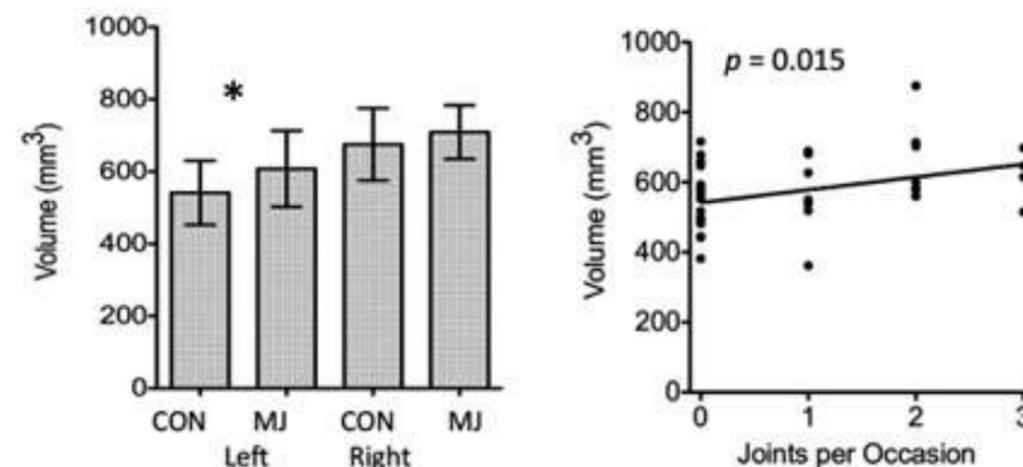
A Gray Matter Density: Marijuana > Control Participants



B Associations Drug Use Behavior and Gray Matter Density in Left Nucleus Accumbens



C Volume and Associations with Drug Use in Left Nucleus Accumbens



Drugs • April 2014

**Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®):
a review of its use in patients with moderate to severe spasticity due to multiple sclerosis**

Syed YY1, McKeage K, Scott LJ.

1. Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore, 0754, Auckland, New Zealand
demail@springer.com

<http://www.ncbi.nlm.nih.gov/pubmed/24671907>

Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) [Sativex®] is an oromucosal spray formulation that contains principally THC and CBD at an approximately 1:1 fixed ratio, derived from cloned *Cannabis sativa* L. plants. The main active substance, THC, acts as a partial agonist at human cannabinoid receptors (CB1 and CB2), and thus, may modulate the effects of excitatory (glutamate) and inhibitory (gamma-aminobutyric acid) neurotransmitters. THC/CBD is approved in a number of countries, including Germany and the UK, as an add-on treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. In the largest multinational clinical trial that evaluated the approved THC/CBD regimen in this population, 12 weeks' double-blind treatment with THC/CBD significantly reduced spasticity severity (primary endpoint) compared with placebo in patients who achieved a clinically significant improvement in spasticity after 4 weeks' single-blind THC/CBD treatment, as assessed by a patient-rated numerical rating scale. A significantly greater proportion of THC/CBD than placebo recipients achieved a $\geq 30\%$ reduction (a clinically relevant reduction) in spasticity severity. The efficacy of THC/CBD has been also shown in at least one everyday clinical practice study (MOVE 2). THC/CBD was generally well tolerated in clinical trials. Dizziness and fatigue were reported most frequently during the first 4 weeks of treatment and resolved within a few days even with continued treatment. Thus, add-on THC/CBD is a useful symptomatic treatment option for its approved indication.

The Effect of Medical Marijuana Laws on Crime: Evidence from State Panel Data, 1990-2006

Robert G. Morris,* Michael TenEyck, J. C. Barnes, and Tomislav V. Kovandzic

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3966811/>

Debate has surrounded the legalization of marijuana for medical purposes for decades. Some have argued medical marijuana legalization (MML) poses a threat to public health and safety, perhaps also affecting crime rates. In recent years, some U.S. states have legalized marijuana for medical purposes, reigniting political and public interest in the impact of marijuana legalization on a range of outcomes.

Relying on U.S. state panel data, we analyzed the association between state MML and state crime rates for all Part I offenses collected by the FBI.

Results did not indicate a crime exacerbating effect of MML on any of the Part I offenses. Alternatively, state MML may be correlated with a reduction in homicide and assault rates, net of other covariates.

These findings run counter to arguments suggesting the legalization of marijuana for medical purposes poses a danger to public health in terms of exposure to violent crime and property crimes.

Investigation of cannabis biomarkers and transformation products in waters by liquid chromatography coupled to time of flight and triple quadrupole mass spectrometry

Boix C1, Ibáñez M1, Bijlsma L1, Sancho JV1, Hernández F2.

1,2. Research Institute for Pesticides and Water, University Jaume I, Avda. Sos Baynat, E-12071 Castellón, Spain
Electronic address: felix.hernandez@uji.es

<http://www.ncbi.nlm.nih.gov/pubmed/24216262>

11-Nor-9-carboxy- Δ (9)-tetrahydrocannabinol (THC-COOH) is commonly selected as biomarker for the investigation of cannabis consumption through wastewater analysis.

The removal efficiency of THC-COOH in wastewater treatment plants (WWTPs) has been reported to vary between 31% and 98%.

Accordingly, possible transformation products (TPs) of this metabolite might be formed during treatment processes or in receiving surface water under environmental conditions. In this work, surface water was spiked with THC-COOH and subjected to hydrolysis, chlorination and photo-degradation (both ultraviolet and simulated sunlight) experiments under laboratory-controlled conditions. One hydrolysis, eight chlorination, three ultraviolet photo-degradation and seven sunlight photo-degradation TPs were tentatively identified by liquid chromatography coupled to quadrupole time-of-flight mass spectrometer (LC-QTOF MS). In a subsequent step, THC-COOH and the identified TPs were searched in wastewater samples using LC coupled to tandem mass spectrometry (LC-MS/MS) with triple quadrupole. THC-COOH was found in all influent and effluent wastewater samples analyzed, although at significant lower concentrations in the effluent samples. The removal efficiency of WWTP under study was approximately 86%. Furthermore, THC-COOH was also investigated in several surface waters, and it was detected in 50% of the samples analyzed. Regarding TPs, none were found in influent wastewater, while one hydrolysis and five photo-degradation (simulated sunlight) TPs were detected in effluent and surface waters. The most detected compound, resulting from sunlight photo-degradation, was found in 60% of surface waters analyzed. This fact illustrates the importance of investigating these TPs in the aquatic environment.

Effects of hemp (*Cannabis sativa* L.) seed oil press-cake and decaffeinated green tea leaves (*Camellia sinensis*) on functional characteristics of gluten-free crackers

Radočaj O1, Dimić E, Tsao R.

Faculty of Technology, Univ. of Novi Sad, Bulevar cara Lazara 1, 21000, Novi Sad, Serbia

<http://www.ncbi.nlm.nih.gov/pubmed/24527987>

A mixture, simplex centroid, 2 components experimental design was used to evaluate the addition of hemp seed oil press-cake and decaffeinated green tea leaves, as functional ingredients to assess nutritional characteristics and antioxidant properties of gluten-free crackers.

All samples with added hemp flour had much better nutritional qualities than the brown rice flour crackers in terms of higher protein, crude fibers, minerals, and essential fatty acids content. Likewise, all samples with added decaffeinated green tea leaves had much better antioxidant properties than crackers with no added green tea leaves.

All crackers with added hemp flour had a significantly increased fiber content (39% to 249%) and decreased carbohydrate content (8.4% to 42.3%), compared to the brown rice flour crackers.

All samples had antioxidant properties, even without the addition of green tea leaves. Optimization of the responses was conducted based on the maximized values for protein, fibers, omega-3 fatty acids content, as well as for the antioxidant activity and overall score.

Hemp seed oil press-cake as a by-product of cold-pressed oil processing and brown rice flour were used to design a functional gluten-free snack-type product-savory crackers. All crackers were high in minerals, fibers, and omega-3 fatty acids with a desirable omega-6/omega-3 fatty acids ratio. Green tea leaves were added to improve antioxidant activity, which greatly contributed to their functional properties. This qualified the crackers as a healthy snack with a minimal content saturated fatty acids and an abundance of polyunsaturated and monounsaturated fatty acids that originated from chia seeds residual oil present in the hemp flour.

Current Opinions In Pulmonary Medicine • March 2014

Marijuana and lung diseases

Joshi M1, Joshi A, Bartter T.

University of Arkansas for Medical Sciences bCentral Arkansas, Veterans Healthcare System, Little Rock, Arkansas, USA

<http://www.ncbi.nlm.nih.gov/pubmed/24384575>

Cannabis sativa (marijuana) is used throughout the world, and its use is increasing. In much of the world, marijuana is illicit. While inhalation of smoke generated by igniting dried components of the plant is the most common way marijuana is used, there is concern over potential adverse lung effects. The purpose of this review is to highlight recent studies that explore the impact upon the respiratory system of inhaling marijuana smoke.

Smoking marijuana is associated with chronic bronchitis symptoms and large airway inflammation. Occasional use of marijuana with low cumulative use is not a risk factor for the development of chronic obstructive pulmonary disease. The heavy use of marijuana alone may lead to airflow obstruction. The immuno-histopathologic and epidemiologic evidence in marijuana users suggests biological plausibility of marijuana smoking as a risk for the development of lung cancer; at present, it has been difficult to conclusively link marijuana smoking and cancer development.

There is unequivocal evidence that habitual or regular marijuana smoking is not harmless. A caution against regular heavy marijuana usage is prudent. The medicinal use of marijuana is likely not harmful to lungs in low cumulative doses, but the dose limit needs to be defined. Recreational use is not the same as medicinal use and should be discouraged.

Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease

Storr M1, Devlin S, Kaplan GG, Panaccione R, Andrews CN.

¹*Division of Gastroenterology, Department of Medicine, University of Calgary and

†Division of Gastroenterology, Department of Medicine, University of Munich

<http://www.ncbi.nlm.nih.gov/pubmed/24407485>

Cannabinoids are used by patients with inflammatory bowel disease (IBD) to alleviate their symptoms. Little is known on patient motivation, benefit, or risks of this practice. Our aim was to assess the extent and motives for Cannabis use in patients with IBD and the beneficial and adverse effects associated with self-administration of Cannabis.

Consecutive patients with IBD (n = 313) seen in the University of Calgary from July 2008 to March 2009 completed a structured anonymous questionnaire covering motives, pattern of use, and subjective beneficial and adverse effects associated with self-administration of Cannabis. Subjects who had used Cannabis specifically for the treatment of IBD or its symptoms were compared with those who had not. Logistic regression analysis was used to identify variables predictive of poor IBD outcomes, specifically surgery or hospitalization for IBD.

Cannabis had been used by 17.6% of respondents specifically to relieve symptoms associated with their IBD, the majority by inhalational route (96.4%). Patients with IBD reported that Cannabis improved abdominal pain (83.9%), abdominal cramping (76.8%), joint pain (48.2%), and diarrhea (28.6%), although side effects were frequent. The use of Cannabis for more than 6 months at any time for IBD symptoms was a strong predictor of requiring surgery in patients with Crohn's disease (odds ratio = 5.03, 95% confidence interval = 1.45-17.46) after correcting for demographic factors, tobacco smoking status, time since IBD diagnosis, and biological use. Cannabis was not a predictor for hospitalization for IBD in the previous year.

Cannabis use is common in patients with IBD and subjectively improved pain and diarrheal symptoms. However, Cannabis use was associated with higher risk of surgery in patients with Crohn's disease. Patients using Cannabis should be cautioned about potential harm, until clinical trials evaluate efficacy and safety.

IBD: Patients with IBD find symptom relief in the Cannabis field

Schicho R1, Storr M2.

1. Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Universitätsplatz 4, 8010 Graz, Austria
2. Department of Medicine II, Klinikum Grosshadern, Ludwig-Maximilians University, Marchioninistrasse 15, 81377 Munich, Germany

Full text with 10 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3947743/>

Cannabis (or marijuana) has been used in traditional medicine to treat intestinal inflammation and is used as a self-medication by patients with inflammatory bowel disease (IBD). A survey by Ravikoff Allegretti et al. 1 at a specialized IBD clinic shows that, in the US, marijuana is used by a significant number of patients with IBD to alleviate their symptoms.

In gastroenterology, Cannabis is known for its antiemetic, appetite stimulating and antidiarrheal effects. Despite the well-characterized impact of cannabinoids in experimental intestinal inflammation,² knowledge on the potential benefits of cannabinoids in human IBD is largely based on anecdotal reports. There is strong evidence from basic science that cannabinoids protect against and alleviate intestinal inflammation in mice, but for human IBD, cannabinoid effects remain to be established yet in clinical trials. Ravikoff Allegretti et al. have presented a prospective survey study on 292 IBD patients revealing that a significant number of IBD patients in the US

(16.4 %) have used Cannabis to treat symptoms, such as abdominal pain, loss of appetite, nausea and diarrhea.¹ The majority of the patients reported that Cannabis was “very helpful” in reducing these symptoms. A further important aspect of their study was that not only patients with Crohn’s disease but also patients with ulcerative colitis classified Cannabis as “very helpful”. Using multivariate analysis, the authors further identified that age and abdominal pain were the strongest predictors for the use of Cannabis in IBD patients. Without doubt, the present survey supports the traditional view that Cannabis provides benefit in disturbances of the gastrointestinal tract, especially in abdominal pain.

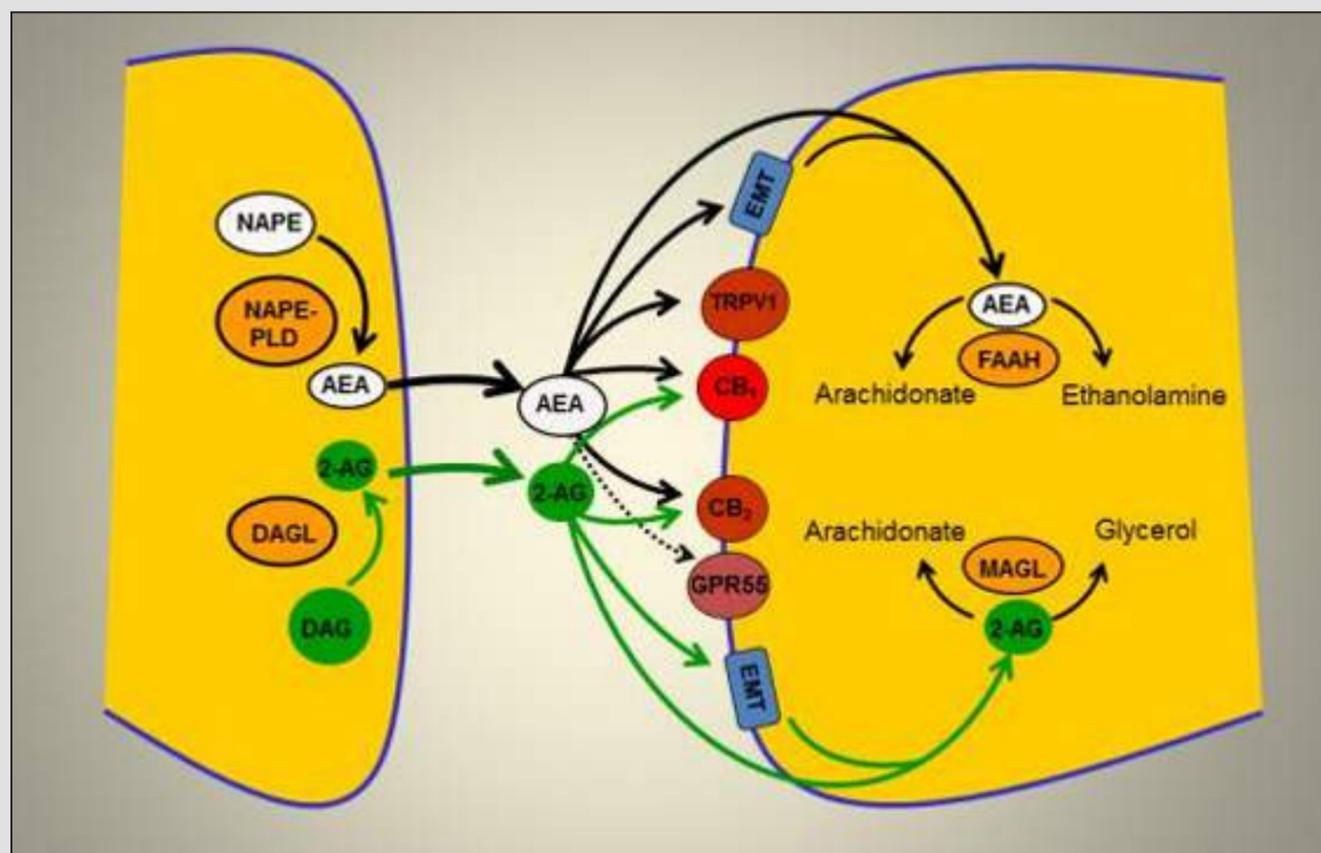
Their results confirm a 2011 published survey in a Canadian population by Lal et al. in which chronic abdominal pain and a history of abdominal surgery were reported as primary reasons for the use of Cannabis.³ One prospective uncontrolled observational study already found improved quality of life and

reductions of disease activity in patients with IBD who were advised to smoke cigarettes with Cannabis, whenever they felt pain.⁴ Thirteen patients were included and were provided with 50 g dry Cannabis per month for the on demand treatment. All patients used the full amount and additional use of Cannabis was not captured. A recently published prospective placebo controlled clinical trial by Naftali et al. where patients with Crohn's disease received two cigarettes with 11.5 mg tetrahydrocannabinol (THC) per day for 8 weeks found significant clinical benefits in the THC-treated patients in the secondary analyses but the primary end point of induction of remission was not achieved.⁵ Interestingly, no relevant side effects were reported.^{4,5} From both studies we learn that there may be a

role for Cannabis in the treatment of IBD but further information may help to select the right group of patients for which Cannabis may be beneficial. Cannabis may help in Crohn's disease, ulcerative colitis or in both, in induction or maintenance of remission of these diseases. Thus, epidemiological data are needed to direct future clinical trials.

Scheme of the endocannabinoid system

The endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are synthesized and released on demand in a paracrine fashion. N-arachidonoylphosphatidylethanolamine (NAPE) needs arachidonic acid as a precursor and is cleaved by a phospholipase D (NAPE-PLD) into AEA. The key enzyme in synthesizing 2-AG from diacylglycerol (DAG) is diacylglycerol lipase (DAGL). AEA and 2-AG primarily activate cannabinoid receptors (cannabinoid receptor 1 and 2; CB₁, CB₂) but AEA may also act as a ligand for the transient receptor potential cation channel 1 (vanilloid receptor 1; TRPV1) and the G protein-coupled receptor 55 (GPR55). The existence of an endocannabinoid transporter (EMT) is still controversial. The main enzyme in degrading AEA is fatty acid amide hydrolase (FAAH) while 2-AG is degraded by monoacylglycerol lipase (MAGL). The EMT, the GPR55 and the TRPV1 receptor may not be part of the endocannabinoid system in a close sense but were added to the system as they are responsive to and involved in the action of exo- and endocannabinoids.



La Revue du Praticien • February 2014

Therapeutic use of cannabis derivatives

Benyamina A, Reynaud M.

<http://www.ncbi.nlm.nih.gov/pubmed/24701869>

The therapeutic use of cannabis has generated a lot of interest in the past years, leading to a better understanding of its mechanisms of action. Countries like the United States and Canada have modified their laws in order to make cannabinoid use legal in the medical context. It's also the case in France now, where a recent decree was issued, authorizing the prescription of medication containing "therapeutic cannabis" (decree no. 2013-473, June 5, 2013). Cannabinoids such as dronabinol, Sativex and nabilone have been tested for the treatment of acute and chronic pain. These agents are most promising to relieve chronic pain associated with cancer, with human immunodeficiency virus infection and with multiple sclerosis. However, longer-term studies are required to determine potential long-term adverse effects and risks of misuse and addiction.

Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation

Stone JM1, Fisher HL2, Major B3, Chisholm B4, Woolley J4, Lawrence J5, Rahaman N6, Joyce J7, Hinton M8, Johnson S8, Young AH1; MiData Consortium.

1. Imperial College London, London, UK
2. Institute of Psychiatry, King's College London, London, UK
3. EQUIP, East London NHS Foundation Trust, London, UK
4. Wandsworth Early Intervention Service, South West London and St George's Mental Health NHS Trust, London, UK
5. Southwark Early Intervention Service, South London and Maudsley NHS Foundation Trust, London, UK
6. Westminster and Kensington & Chelsea Early Intervention Service, London, UK
7. Lewisham Early Intervention Service, London, UK
8. University College London, London, UK

<http://www.ncbi.nlm.nih.gov/pubmed/23701858>

Cannabis use has been reported to be associated with an earlier onset of symptoms in patients with first-episode psychosis, and a worse outcome in those who continue to take cannabis. In general, studies have concentrated on symptoms of psychosis rather than mania. In this study, using a longitudinal design in a large naturalistic cohort of patients with first-episode psychosis, we investigated the relationship between cannabis use, age of presentation to services, daily functioning, and positive, negative and manic symptoms.

Level of cannabis use was associated with a younger age at presentation, and manic symptoms and conceptual disorganization, but not with delusions, hallucinations, negative symptoms or daily functioning. Cannabis users who reduced or stopped their use following contact with services had the greatest improvement in symptoms at 1 year compared with continued users and non-users. Continued users remained more symptomatic than non-users at follow-up.

Effective interventions for reducing cannabis use may yield significant health benefits for patients with first-episode psychosis.

Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system

Sharkey KA1, Darmani NA2, Parker LA3.

1. Hotchkiss Brain Institute, Department of Physiology and Pharmacology, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada
 2. Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, USA
 3. Department of Psychology, University of Guelph, Guelph, ON, Canada
- Electronic address: ksharkey@ucalgary.ca

Full text with 199 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883513/>

Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions.

Drug Testing And Analysis • January 2014

The adverse health effects of chronic cannabis use

Hall W1, Degenhardt L.

The University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital Site, Herston, QLD, 4029, Australia
National Addiction Centre, Kings College London, London, WC2R 2LS, UK

<http://www.ncbi.nlm.nih.gov/pubmed/23836598>

This paper summarizes the most probable of the adverse health effects of regular cannabis use sustained over years, as indicated by epidemiological studies that have established an association between cannabis use and adverse outcomes; ruled out reverse causation; and controlled for plausible alternative explanations. We have also focused on adverse outcomes for which there is good evidence of biological plausibility. The focus is on those adverse health effects of greatest potential public health significance--those that are most likely to occur and to affect a substantial proportion of regular cannabis users. These most probable adverse effects of regular use include a dependence syndrome, impaired respiratory function, cardiovascular disease, adverse effects on adolescent psychosocial development and mental health, and residual cognitive impairment.

European Neuropsychopharmacology • January 2014

Cannabidiol as a potential treatment for psychosis

C.D. Schubart, I.E.C. Sommer, P. Fusar-Poli, L. de Witte, R.S. Kahn, M.P.M. Boks

[http://www.europeanneuropsychopharmacology.com/article/S0924-977X\(13\)00332-5/abstract](http://www.europeanneuropsychopharmacology.com/article/S0924-977X(13)00332-5/abstract)

Although cannabis use is associated with an increased risk of developing psychosis, the cannabis constituent cannabidiol (CBD) may have antipsychotic properties. This review concisely describes the role of the endocannabinoid system in the development of psychosis and provides an overview of currently available animal, human experimental, imaging, epidemiological and clinical studies that investigated the antipsychotic properties of CBD. In this targeted literature review we performed a search for English articles using Medline and EMBASE. Studies were selected if they described experiments with psychosis models, psychotic symptoms or psychotic disorders as outcome measure and involved the use of CBD as intervention. Evidence from several research domains suggests that CBD shows potential for antipsychotic treatment.

Drug Test Analysis • January 2014

Therapeutic potential of cannabinoid medicines

By P. J. Robson

Cannabinoid Research Institute, GW Research Ltd, Porton Down Science Park, Salisbury, SP4 0JQ, UK

<http://www.ncbi.nlm.nih.gov/pubmed/24006213>

Cannabis was extensively used as a medicine throughout the developed world in the nineteenth century but went into decline early in the twentieth century ahead of its emergence as the most widely used illicit recreational drug later that century. Recent advances in cannabinoid pharmacology alongside the discovery of the endocannabinoid system (ECS) have re-ignited interest in cannabis-based medicines. The ECS has emerged as an important physiological system and plausible target for new medicines. Its receptors and endogenous ligands play a vital modulatory role in diverse functions including immune response, food intake, cognition, emotion, perception, behavioural reinforcement, motor co-ordination, body temperature, wake/sleep cycle, bone formation and resorption, and various aspects of hormonal control. In disease it may act as part of the physiological response or as a component of the underlying pathology. In the forefront of clinical research are the cannabinoids delta-9-tetrahydrocannabinol and cannabidiol, and their contrasting pharmacology will be briefly outlined. The therapeutic potential and possible risks of drugs that inhibit the ECS will also be considered. This paper will then go on to review clinical research exploring the potential of cannabinoid medicines in the following indications: symptomatic relief in multiple sclerosis, chronic neuropathic pain, intractable nausea and vomiting, loss of appetite and weight in the context of cancer or AIDS, psychosis, epilepsy, addiction, and metabolic disorders.

Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of Cannabis sativa

de Mello Schier AR, de Oliveira Ribeiro NP, Coutinho DS, Machado S, Arias-Carrión O, Crippa JA, Zuardi AW, Nardi AE, Silva AC1.

1. Institute of Psychiatry - Federal University of Rio de Janeiro. Laboratory of Panic and Respiration, Rua Visconde de Pirajá, 407/702, Rio de Janeiro, RJ. CEP 22410-003, Brazil
alexschier@hotmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/24923339>

Anxiety and depression are pathologies that affect human beings in many aspects of life, including social life, productivity and health. Cannabidiol (CBD) is a constituent non-psychotomimetic of Cannabis sativa with great psychiatric potential, including uses as an antidepressant-like and anxiolytic-like compound. The aim of this study is to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound. Studies involving animal models, performing a variety of experiments on the above-mentioned disorders, such as the forced swimming test (FST), elevated plus maze (EPM) and Vogel conflict test (VCT), suggest that CBD exhibited an anti-anxiety and antidepressant effects in animal models discussed. Experiments with CBD demonstrated non-activation of neuroreceptors CB1 and CB2. Most of the studies demonstrated a good interaction between CBD and the 5-HT1A neuro-receptor.



CANNABIS • 2013 PEER REVIEW

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Porter BE1, Jacobson C.

Department of Neurology, Stanford University, USA

Full text with 23 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157067/>

Severe childhood epilepsies are characterized by frequent seizures, neurodevelopmental delays, and impaired quality of life. In these treatment-resistant epilepsies, families often seek alternative treatments. This survey explored the use of cannabidiol-enriched cannabis in children with treatment-resistant epilepsy. The survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of cannabidiol-enriched cannabis to treat their child's seizures. Nineteen responses met the following inclusion criteria for the study: a diagnosis of epilepsy and current use of cannabidiol-enriched cannabis.

Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy. The average number of antiepileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12.

Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25-60% seizure reduction.

Other beneficial effects included increased alertness, better mood, and improved sleep. Side effects included drowsiness and fatigue. Our survey shows that parents are using cannabidiol-enriched cannabis as a treatment for their children with treatment-resistant epilepsy. Because of the increasing number of states that allow access to medical cannabis, its use will likely be a growing concern for the epilepsy community. Safety and tolerability data for cannabidiol-enriched cannabis use among children are not available. Objective measurements of a standardized preparation of pure cannabidiol are needed to determine whether it is safe, well tolerated, and efficacious at controlling seizures in this pediatric population with difficult-to-treat seizures.

Harefuah • December 2013

Short-and long-term effects of cannabinoids on memory, cognition and mental illness

Sagie S1, Eliasi Y2, Livneh I3, Bart Y2, Monovich E2.

1. MoLecular Medicine Laboratory, Technion-Israel Institute of Technology, Haifa, Israel
2. Rappaport Faculty of Medicine and Research Institute, Technion-Israel Institute of Technology, Haifa, Israel
3. Cancer and Vascular Biology Research Center, Technion-Israel Institute of Technology, Haifa, Israel
shirasagie@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/24483000>

Marijuana is considered the most commonly used drug in the world, with estimated millions of users. There is dissent in the medical world about the positive and negative effects of marijuana, and recently, a large research effort has been directed to that domain. The main influencing drug ingredient is THC, which acts on the cannabinoid system and binds to the CB1 receptor. The discovery of the receptor led to the finding of an endogenous ligand, anandamide, and another receptor-CB2. The researchers also discovered that cannabinoids have extensive biological activity, and its short and long-term effects may cause cognitive and emotional deficiencies. Findings show that the short-term effects, such as shortterm memory and verbal Learning, are reversible. However, despite the accumulation of evidence about long-term cognitive damage due to cannabis use, it is difficult to find unequivocal results, arising from the existence of many variables such as large differences between cannabis users, frequency of use, dosage and endogenous brain compensation. Apart from cognitive damage, current studies investigate how marijuana affects mental illness: a high correlation between cannabis use and schizophrenia was found and a high risk to undergo a psychotic attack. Furthermore, patients with schizophrenia who used cannabis showed a selective neuro-psychological disruption, and similar cognitive deficiencies and brain morphological changes were found among healthy cannabis users and schizophrenia patients. In contrast to the negative effects of marijuana including addiction, there are the medical uses: reducing pain, anxiety and nausea, increasing appetite and an anti-inflammatory activity. Medicalization of marijuana encourages frequent use, which may elevate depression.

Cannabidiol enhances xenobiotic permeability through the human placental barrier by direct inhibition of breast cancer resistance protein: an ex vivo study

Feinshtein V1, Erez O, Ben-Zvi Z, Eshkoli T, Sheizaf B, Sheiner E, Holcberg G.

Department of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beer-Sheva, Israel

<http://www.ncbi.nlm.nih.gov/pubmed/23933222>

Drugs of abuse affect pregnancy outcomes, however, the mechanisms in which cannabis exerts its effects are not well understood. The aim of this study was to examine the influence of short-term (1-2 hours) exposure to cannabidiol, a major phytocannabinoid, on human placental breast cancer resistance protein function.

(1) Cannabidoil inhibition of breast cancer resistance protein-dependent mitoxantrone efflux was concentration dependent and of a noncell type specific nature ($P < .0001$);

(2) In the cotyledon perfusion assay, the administration of cannabidoil to the maternal perfusion media increased the female/male ratio of glyburide concentrations (1.3 ± 0.1 vs 0.8 ± 0.1 at 120 minutes of perfusion, $P < .001$).

(1) Placental breast cancer resistance protein function is inhibited following even a short-term exposure to cannabidoil;

(2) the ex vivo perfusion assay emphasize this effect by increased placental penetration of glyburide to the fetal compartment; and

(3) these findings suggest that marijuana consumption enhances placental barrier permeability to xenobiotics and could endanger the developing fetus. Thus, the safety of drugs that are breast cancer resistance protein substrates is questionable during cannabis consumption by pregnant women.

Yakugaku Zasshi • December 2013

Medicinal chemistry and pharmacology focused on cannabidiol, a major component of the fiber-type cannabis

By S. Takeda

Department of Molecular Biology, Daiichi University of Pharmacy

Full text, PDF, with 34 references, in Japanese

https://www.jstage.jst.go.jp/article/yakushi/133/10/133_13-00196/_pdf

Abstract in English

https://www.jstage.jst.go.jp/article/yakushi/133/10/133_13-00196/_article/-char/ja/

Considerable attention has focused on cannabidiol (CBD), a major non-psychotropic constituent of fiber-type cannabis plant, and it has been reported to possess diverse biological activities. Although CBD is obtained from non-enzymatic decarboxylation of its parent molecule, cannabidiolic acid (CBDA), several studies have investigated whether CBDA itself is biologically active. In the present report, the author summarizes findings indicating that; 1) CBDA is a selective cyclooxygenase-2 (COX-2) inhibitor, and ii) CBDA possesses an anti-migrative potential for highly invasive cancer cells, apparently through a mechanism involving inhibition of cAMP-dependent protein kinase A, coupled with an activation of the small GTPase, RhoA. Further, the author introduces recent findings on the medicinal chemistry and pharmacology of the CBD derivative, CBD-2',6'-dimethyl ether (CBDD), that exhibits inhibitory activity toward 15-lipoxygenase (15-LOX), an enzyme responsible for the production of oxidized low-density lipoprotein (LDL). These studies establish CBD as both an important experimental tool and as a lead compound for pharmaceutical development. In this review, the author further discusses the potential uses of CBD and its derivatives in future medicines.

La Revue du Praticien • December 2013

Somatic consequences of cannabis use

Cottencin O1, Bence C2, Rolland B2, Karila L3.

1,2. CHRU de Lille, hôpital Michel-Fontan 2, service d'addictologie, France

3. Centre de recherche et de traitement des addictions, hôpital Paul-Brousse, AP-HP, 94800 Villejuif, France
olivier.cottencin@chru-lille.fr

<http://www.ncbi.nlm.nih.gov/pubmed/24579346>

Cannabis can have negative effects in its users, and a range of acute and chronic health problems associated with cannabis use has been identified. Acute cannabis consumption is rarely lethal but it is associated with an increased risk of motor vehicle accident because of longer reaction time or impaired motor coordination. Chronic effects of cannabis use include generally cardiovascular and respiratory consequences but there are also oral, gastrointestinal, cutaneous and mucous, metabolic, gynecologic and obstetrical, sexual consequences, and cancer. But associated tobacco smoking or other potential confounders may explain part of those somatic consequences.

Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation

Singh Y1, Bali C2.

1. Brampton, Ont., Canada
2. Ajax, Ont., Canada

Full text with 4 references

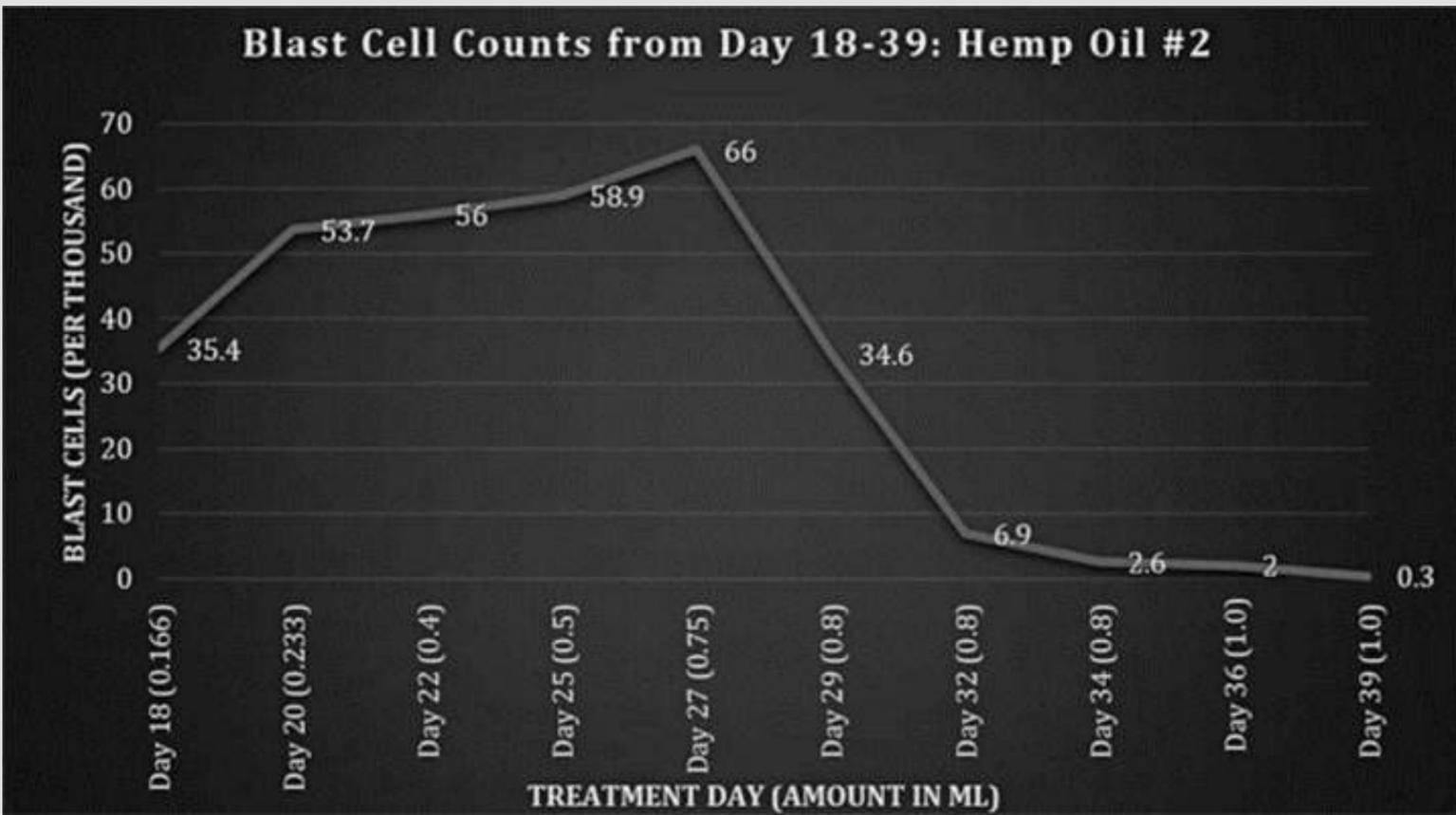
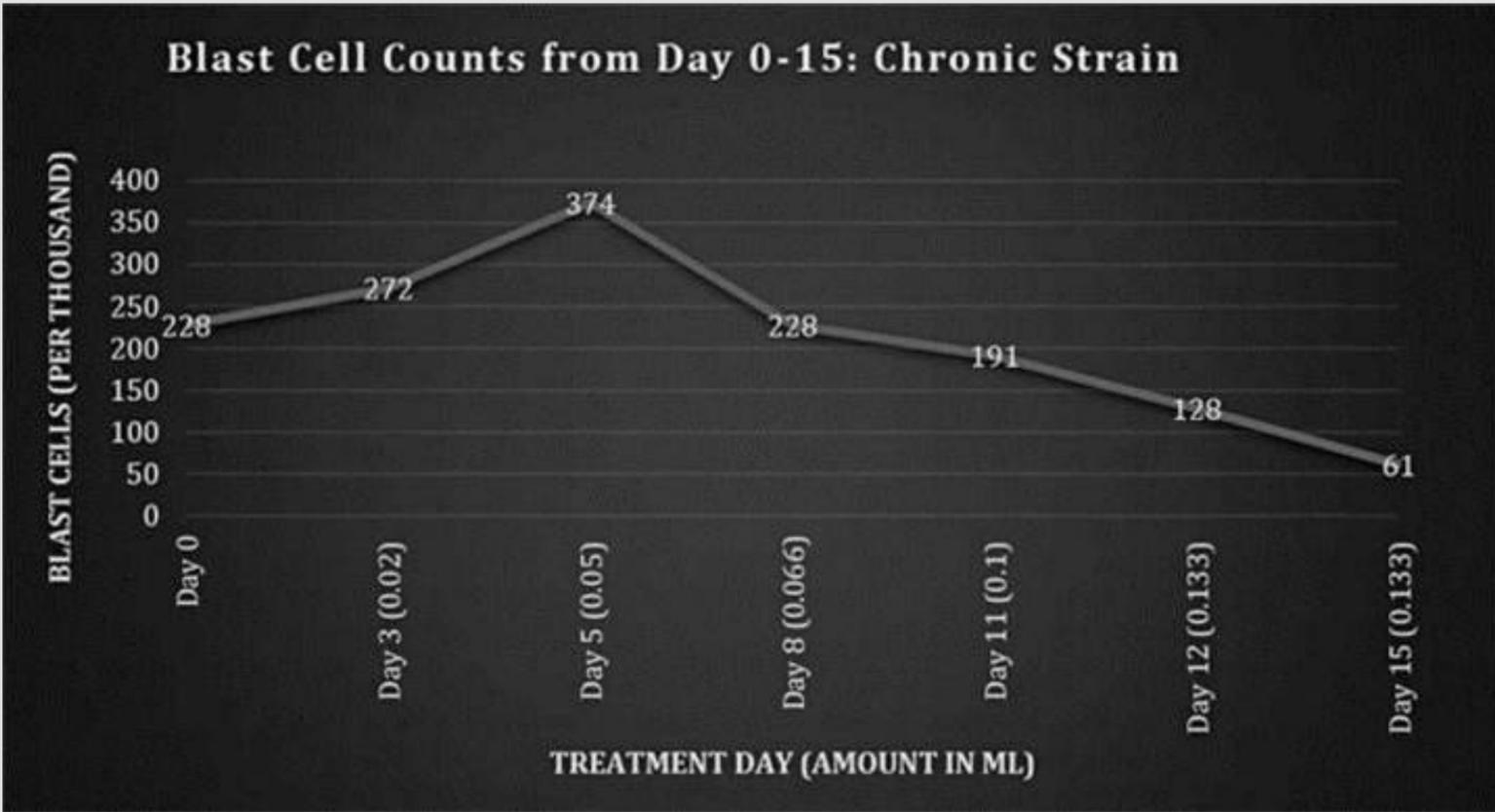
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901602/>

Acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells and is typically well treated with combination chemotherapy, with a remission state after 5 years of 94% in children and 30-40% in adults. To establish how aggressive the disease is, further chromosome testing is required to determine whether the cancer is myeloblastic and involves neutrophils, eosinophils or basophils, or lymphoblastic involving B or T lymphocytes. This case study is on a 14-year-old patient diagnosed with a very aggressive form of ALL (positive for the Philadelphia chromosome mutation).

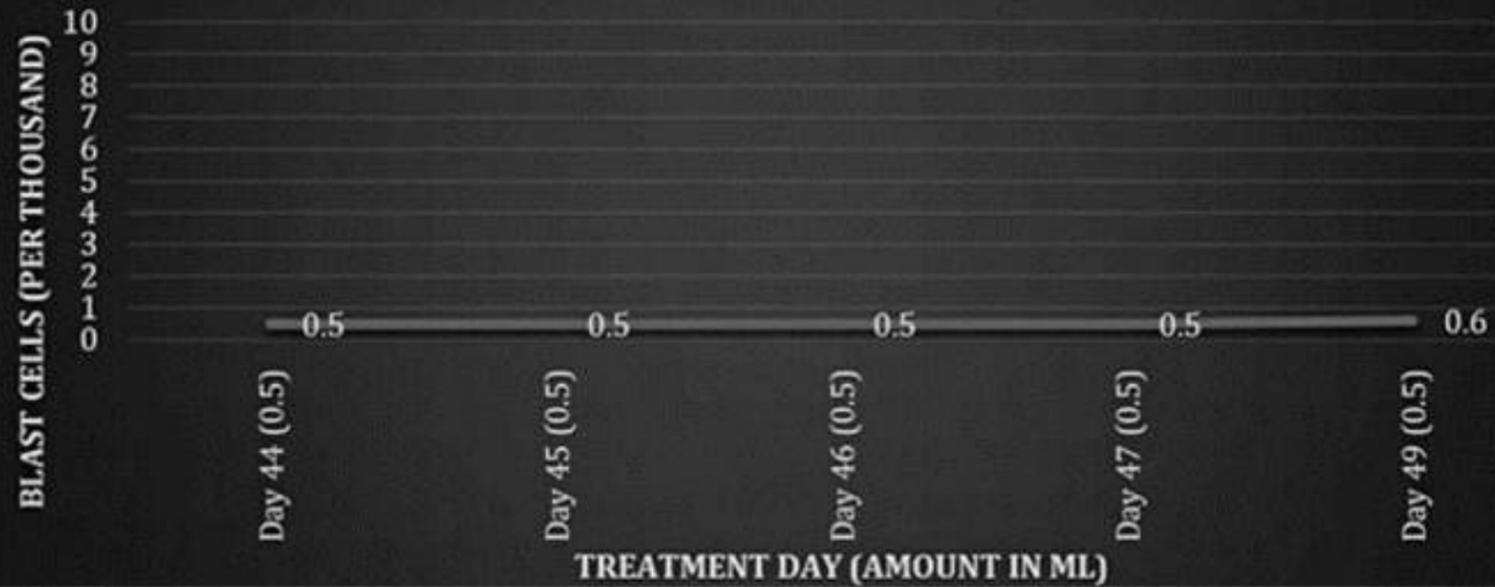
A standard bone marrow transplant, aggressive chemotherapy and radiation therapy were revoked, with treatment being deemed a failure after 34 months.

Without any other solutions provided by conventional approaches aside from palliation, the family administered cannabinoid extracts orally to the patient. Cannabinoid resin extract is used as an effective treatment for ALL with a positive Philadelphia chromosome mutation and indications of dose-dependent disease control. The clinical observation in this study revealed a rapid dose-dependent correlation.

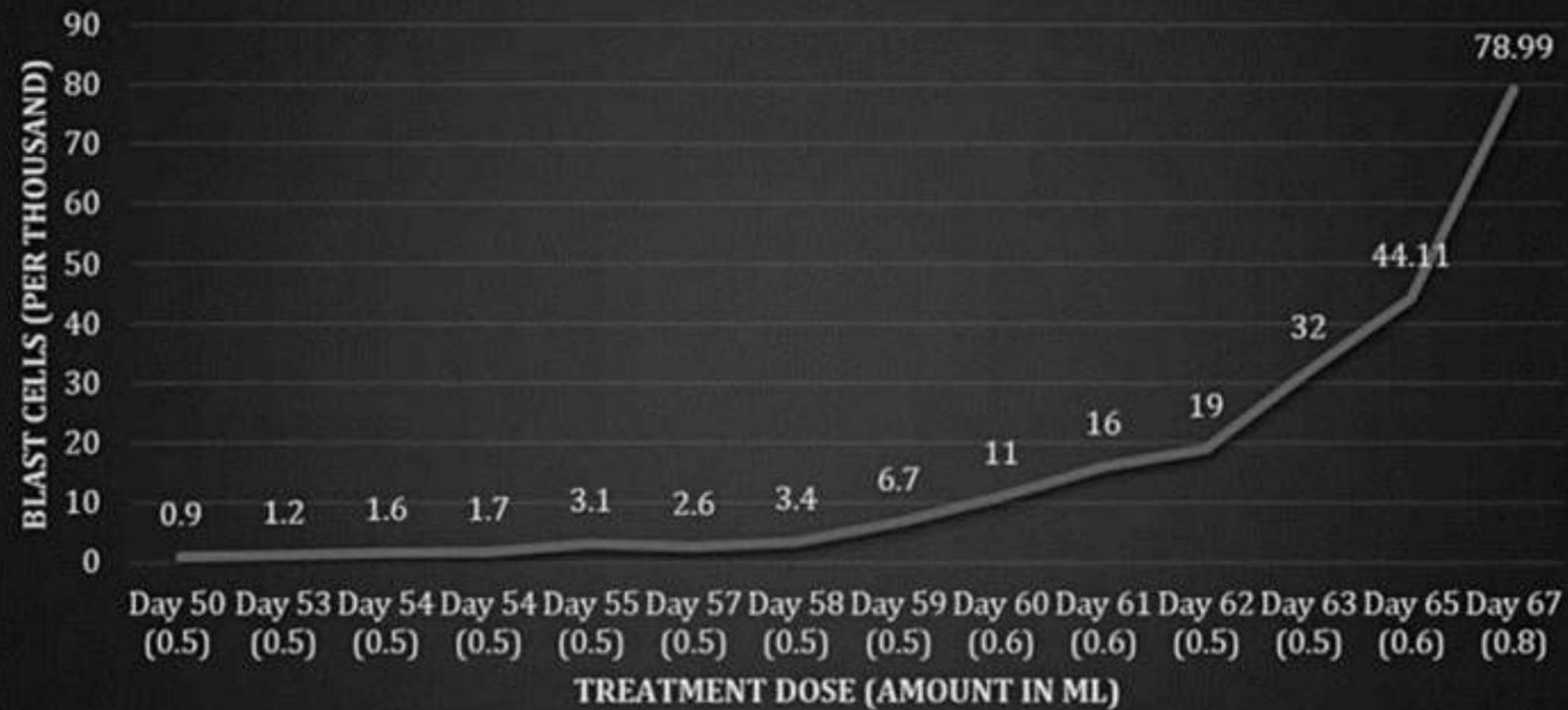
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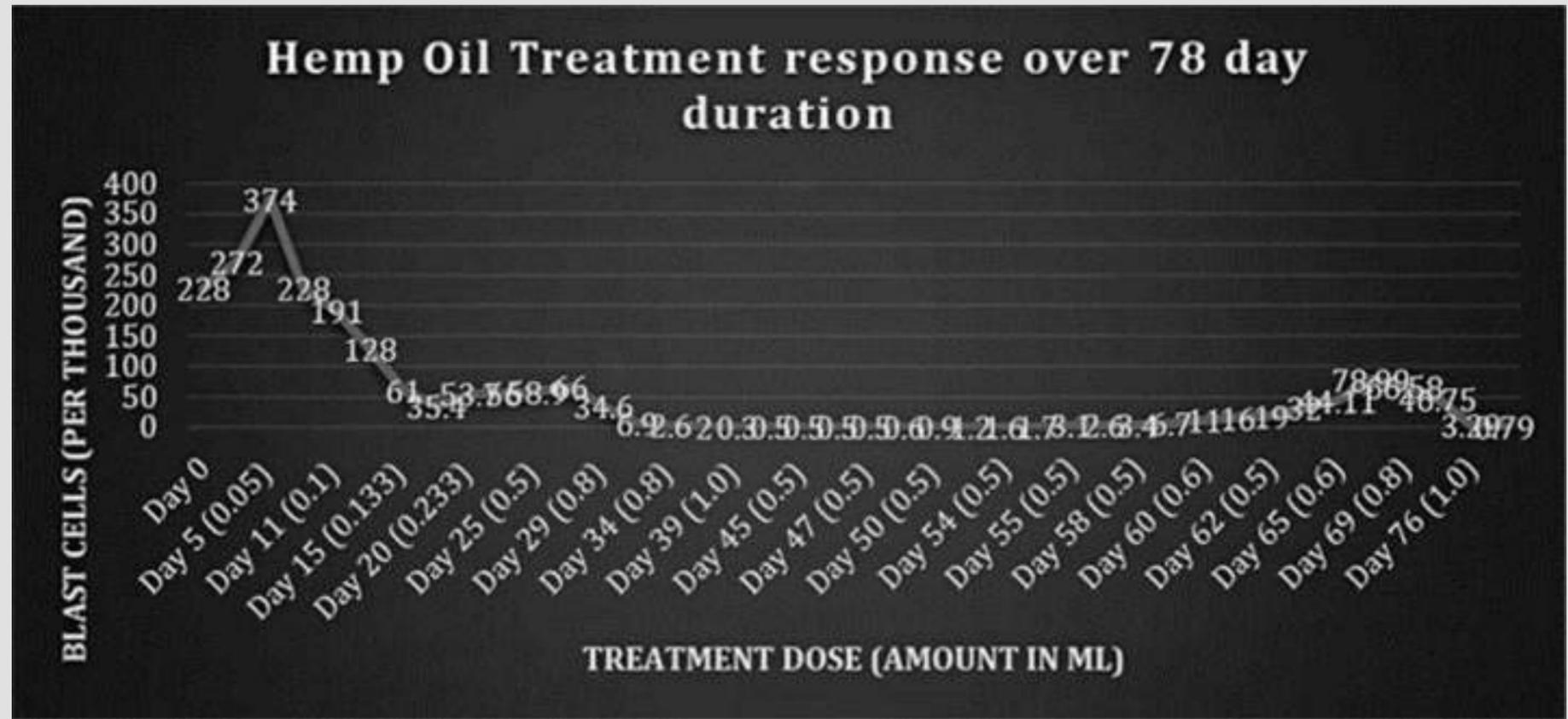
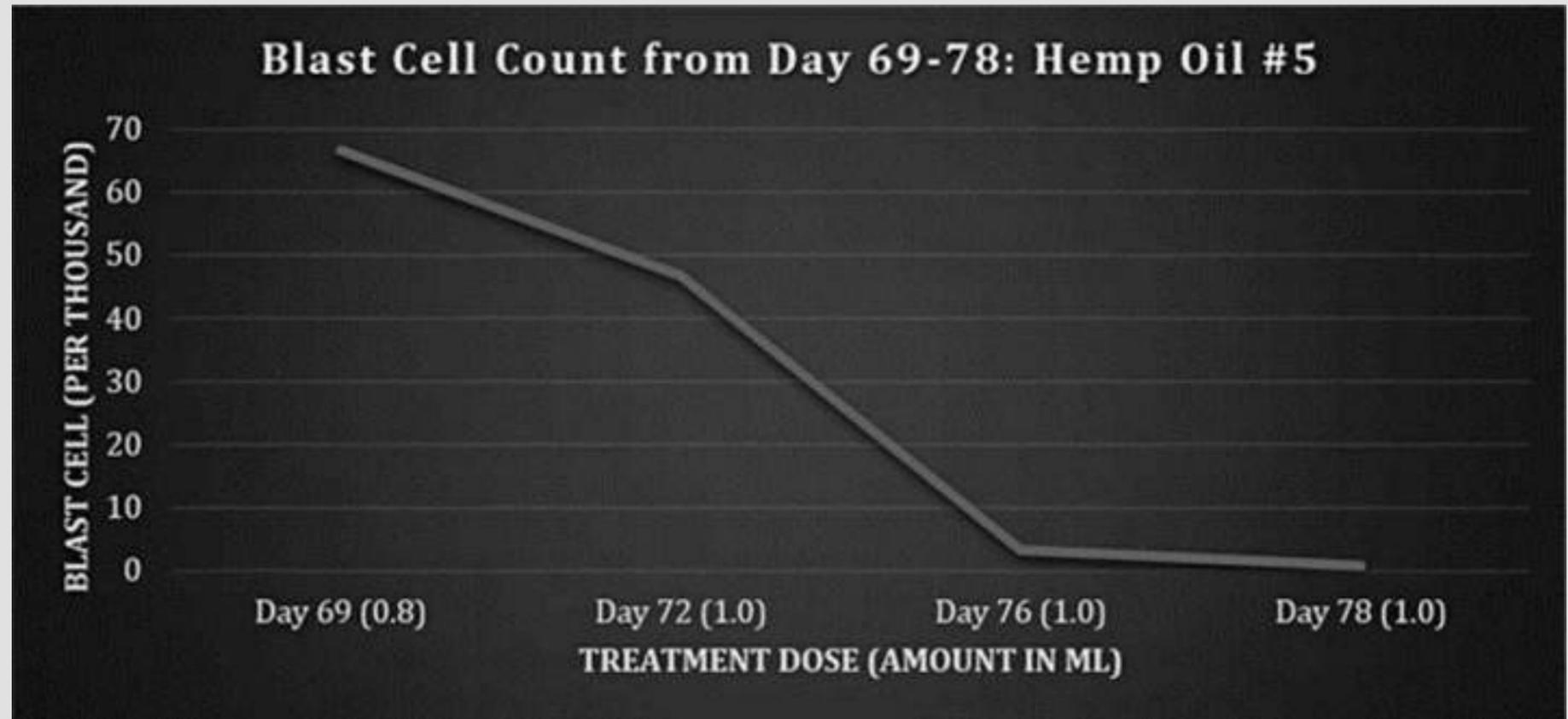


Blast Cell Count from Day 44-49: Hemp Oil #3



Blast Cell Count from Day 50-67: Hemp Oil #4





Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study

Cousijn J1, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Porrino LJ, Goudriaan AE.

ADAPT-lab, Department of Psychology, University of Amsterdam, The Netherlands
Amsterdam Institute for Addiction Research, Department of Psychiatry, Academic Medical Centre, University of Amsterdam, The Netherlands

<http://www.ncbi.nlm.nih.gov/pubmed/22994937>

Decision-making deficits are thought to play an important role in the development and persistence of substance use disorders. Individual differences in decision-making abilities and their underlying neurocircuitry may, therefore, constitute an important predictor for the course of substance use and the development of substance use disorders. Here, we investigate the predictive value of decision making and neural mechanisms underlying decision making for future cannabis use and problem severity in a sample of heavy cannabis users. Brain activity during a monetary decision-making task (Iowa gambling task) was compared between 32 heavy cannabis users and 41 matched non-using controls using functional magnetic resonance imaging. In addition, within the group of heavy cannabis users, associations were examined between task-related brain activations, cannabis use and cannabis use-related problems at baseline, and change in cannabis use and problem severity after a 6-month follow-up. Despite normal task performance, heavy cannabis users compared with controls showed higher activation during wins in core areas associated with decision making. Moreover, within the group of heavy cannabis users, win-related activity and activity anticipating loss outcomes in areas generally involved in executive functions predicted change in cannabis use after 6 months. These findings are consistent with previous studies and point to abnormal processing of motivational information in heavy cannabis users. A new finding is that individuals who are biased toward immediate rewards have a higher probability of increasing drug use, highlighting the importance of the relative balance between motivational processes and regulatory executive processes in the development of substance use disorders.

Marijuana use and risk of lung cancer: a 40-year cohort study

Callaghan RC1, Allebeck P, Sidorchuk A.

Northern Medical Program, University of Northern British Columbia (UNBC), 3333 University Way, Prince George, BC, V2N 4Z9, Canada
russ.callaghan@unbc.ca.

<http://www.ncbi.nlm.nih.gov/pubmed/23846283>

Cannabis (marijuana) smoke and tobacco smoke contain many of the same potent carcinogens, but a critical-yet unresolved-medical and public-health issue is whether cannabis smoking might facilitate the development of lung cancer. The current study aimed to assess the risk of lung cancer among young marijuana users.

A population-based cohort study examined men (n = 49,321) aged 18-20 years old assessed for cannabis use and other relevant variables during military conscription in Sweden in 1969-1970. Participants were tracked until 2009 for incident lung cancer outcomes in nationwide linked medical registries. Cox regression modeling assessed relationships between cannabis smoking, measured at conscription, and the hazard of subsequently receiving a lung cancer diagnosis.

At the baseline conscription assessment, 10.5 % (n = 5,156) reported lifetime use of marijuana and 1.7 % (n = 831) indicated lifetime use of more than 50 times, designated as “heavy” use. **Cox regression analyses (n = 44,284) found that such “heavy” cannabis smoking was significantly associated with more than a twofold risk (hazard ratio 2.12, 95 % CI 1.08-4.14) of developing lung cancer over the 40-year follow-up period, even after statistical adjustment for baseline tobacco use, alcohol use, respiratory conditions, and socioeconomic status.**

Our primary finding provides initial longitudinal evidence that cannabis use might elevate the risk of lung cancer. In light of the widespread use of marijuana, especially among adolescents and young adults, our study provides important data for informing the risk-benefit calculus of marijuana smoking in medical, public-health, and drug-policy settings.

Does Cannabidiol Protect Against Adverse Psychological Effects of THC?

Niesink RJ1, van Laar MW.

Trimbos Institute, Netherlands Institute of Mental Health and Addiction, Utrecht, Netherlands
Faculty of Natural Sciences, Open University of the Netherlands, Heerlen, Netherlands

<http://www.ncbi.nlm.nih.gov/pubmed/24137134>

The recreational use of cannabis can have persistent adverse effects on mental health. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive constituent of cannabis, and most, if not all, of the effects associated with the use of cannabis are caused by THC. Recent studies have suggested a possible protective effect of another cannabinoid, cannabidiol (CBD). A literature search was performed in the bibliographic databases PubMed, PsycINFO, and Web of Science using the keyword "cannabidiol." After removing duplicate entries, 1295 unique titles remained. Based on the titles and abstracts, an initial selection was made. The reference lists of the publications identified in this manner were examined for additional references. Cannabis is not a safe drug. Depending on how often someone uses, the age of onset, the potency of the cannabis that is used and someone's individual sensitivity, the recreational use of cannabis may cause permanent psychological disorders. Most recreational users will never be faced with such persistent mental illness, but in some individuals cannabis use leads to undesirable effects: cognitive impairment, anxiety, paranoia, and increased risks of developing chronic psychosis or drug addiction. Studies examining the protective effects of CBD have shown that CBD can counteract the negative effects of THC. However, the question remains of how the laboratory results translate to the types of cannabis that are encountered by real-world recreational users.

British Journal Of Pharmacology • October 2013

Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism

Hill TD1, Cascio MG, Romano B, Duncan M, Pertwee RG, Williams CM, Whalley BJ, Hill AJ.

Reading School of Pharmacy, University of Reading, Reading, UK

Full text with 52 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3792005/>

Epilepsy is the most prevalent neurological disease and is characterized by recurrent seizures. Here, we investigate (i) the anticonvulsant profiles of cannabis-derived botanical drug substances (BDSs) rich in cannabidivarin (CBDV) and containing cannabidiol (CBD) in acute in vivo seizure models and (ii) the binding of CBDV BDSs and their components at cannabinoid CB1 receptors.

CBDV BDSs exerted significant anticonvulsant effects in the pentylenetetrazole ($\geq 100 \text{ mg}\cdot\text{kg}^{-1}$) and audiogenic seizure models ($\geq 87 \text{ mg}\cdot\text{kg}^{-1}$), and suppressed pilocarpine-induced convulsions ($\geq 100 \text{ mg}\cdot\text{kg}^{-1}$). The isobolographic study revealed that the anticonvulsant effects of purified CBDV and CBD were linearly additive when co-administered. Some motor effects of CBDV BDSs were observed on static beam performance; no effects on grip strength were found. The $\Delta(9)$ -tetrahydrocannabinol and $\Delta(9)$ -tetrahydrocannabivarin content of CBDV BDS accounted for its greater affinity for CB1 cannabinoid receptors than purified CBDV.

CBDV BDSs exerted significant anticonvulsant effects in three models of seizure that were not mediated by the CB1 cannabinoid receptor and were of comparable efficacy with purified CBDV. These findings strongly support the further clinical development of CBDV BDSs for the treatment of epilepsy.

Erythrocyte membrane fatty acids in multiple sclerosis patients and hot-nature dietary intervention with co-supplemented hemp-seed and evening-primrose oils

Rezapour-Firouzi S1, Arefhosseini SR, Ebrahimi-Mamaghani M, Farhoudi M, Baradaran B, Ali TM, Zamani F.

School of Nutrition and Health, Tabriz University of Medical Sciences, Iran
Neurosciences Research Center, Tabriz University of Medical Sciences, Iran

Full text with 62 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3847395/>

The risk of developing multiple sclerosis (MS) is associated with increased dietary intake of saturated fatty acids. For many years it has been suspected that this disease might be associated with an imbalance between unsaturated and saturated fatty acids. We determined erythrocyte membrane fatty acids levels in Hot nature dietary intervention with co-supplemented hemp seed and evening primrose oils in multiple sclerosis patients. To determine the erythrocyte membrane fatty acids levels and correlate it with expanded disability status scale (EDSS) at baseline after 6 months intervention in MS patients by gas chromatography, in this double blind, randomized trial, 100 RRMS patients with EDSS<6 were allocated into three groups: "Group A" that received co-supplemented hemp seed and evening primrose oils with advised Hot nature diet. "Group B" received olive oil and "Group C" received the co-supplemented oils. The results showed that the mean follow-up was $180 \pm 2.9SD$ days (N=65, 23 M and 42 F aged 34.25 ± 8.07 years with disease duration of 6.80 ± 4.33 years). There was no significant difference in the study parameters at baseline. After 6 months, EDSS, Immunological parameters and the erythrocyte cell membrane with regard to specific fatty acids showed improvement in the group A and C, whereas there was worsening condition for the group B after the intervention. We concluded that Hot-nature dietary intervention with co-supplemented hemp seed and evening primrose oils caused an increase PUFAs in MS patients and improvement in the erythrocyte membrane fatty acids composition. This could be an indication of restored plasma stores, and a reflection of disease severity reduction.

Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study

Naftali T1, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM.

1. Department of Gastroenterology and Hepatology, Meir Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Kfar Saba, Israel
Electronic address: naftali@post.tau.ac.il.

<http://www.ncbi.nlm.nih.gov/pubmed/23648372>

The marijuana plant *Cannabis sativa* has been reported to produce beneficial effects for patients with inflammatory bowel diseases, but this has not been investigated in controlled trials. We performed a prospective trial to determine whether cannabis can induce remission in patients with Crohn's disease.

We studied 21 patients (mean age, 40 ± 14 y; 13 men) with Crohn's Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti-tumor necrosis factor- α agents. Patients were assigned randomly to groups given cannabis, twice daily, in the form of cigarettes containing 115 mg of Δ 9-tetrahydrocannabinol (THC) or placebo containing cannabis flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and 2 weeks thereafter.

Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; $P = .43$). A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the cannabis group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143 ; $P = .028$). Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects.

Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich cannabis produced significant clinical, steroid-free benefits to 10 of 11 patients with active Crohn's disease, compared with placebo, without side effects. Further studies, with larger patient groups and a nonsmoking mode of intake, are warranted. ClinicalTrials.gov, NCT01040910.

Journal Of Indian Society Of Periodontology • September 2013

Drug addiction and periodontal diseases

Saini GK1, Gupta ND, Prabhat KC.

Department of Periodontology, Bhojia Dental College, Baddi, Himachal Pradesh, India

Full text with 27 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3808011/>

The prevalence of drug addiction is increasing globally. Drug abuse damages many parts of the body such as oral cavity, lungs, liver, brain, heart etc., Addicts suffer from physical, psychological, emotional and behavioral problems. Their nutrition is also compromised. There is certainly an impact of all these factors on the health of periodontium. Dentists should be aware of the effects of drugs while treating the drug addicts. This article correlates the studies done on the impact of abused drugs such as alcohol, tobacco, opiates, cannabis, amphetamines etc., on general and periodontal health.

Critical appraisal of the potential use of cannabinoids in cancer management

Cridge BJ1, Rosengren RJ.

Department of Pharmacology and Toxicology, University of Otago, Dunedin, New Zealand

Full text with 140 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770515/>

Cannabinoids have been attracting a great deal of interest as potential anticancer agents. Originally derived from the plant *Cannabis sativa*, there are now a number of endo-, phyto- and synthetic cannabinoids available. This review summarizes the key literature to date around the actions, antitumor activity, and mechanisms of action for this broad range of compounds. Cannabinoids are largely defined by an ability to activate the cannabinoid receptors - CB1 or CB2. The action of the cannabinoids is very dependent on the exact ligand tested, the dose, and the duration of exposure. Some cannabinoids, synthetic or plant-derived, show potential as therapeutic agents, and evidence across a range of cancers and evidence in vitro and in vivo is starting to be accumulated. Studies have now been conducted in a wide range of cell lines, including glioma, breast, prostate, endothelial, liver, and lung. This work is complemented by an increasing body of evidence from in vivo models. However, many of these results remain contradictory, an issue that is not currently able to be resolved through current knowledge of mechanisms of action. While there is a developing understanding of potential mechanisms of action, with the extracellular signal-regulated kinase pathway emerging as a critical signaling juncture in combination with an important role for ceramide and lipid signaling, the relative importance of each pathway is yet to be determined. The interplay between the intracellular pathways of autophagy versus apoptosis is a recent development that is discussed. Overall, there is still a great deal of conflicting evidence around the future utility of the cannabinoids, natural or synthetic, as therapeutic agents.

Can medical herbs stimulate regeneration or neuroprotection and treat neuropathic pain in chemotherapy-induced peripheral neuropathy?

Schröder S1, Beckmann K, Franconi G, Meyer-Hamme G, Friedemann T, Greten HJ, Rostock M, Efferth T.

1. HanseMercur Center for Traditional Chinese Medicine at the University Medical Center Hamburg-Eppendorf, Martinistrase 52, 20246 Hamburg, Germany
ICBAS, University of Porto, Rua de Jorge Viterbo Ferreira No. 228, 4050-313 Porto, Portugal

Full text with 193 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747437/>

Chemotherapy-induced neuropathy (CIPN) has a relevant impact on the quality of life of cancer patients. There are no curative conventional treatments, so further options have to be investigated. We conducted a systematic review in English and Chinese language databases to illuminate the role of medical herbs. 26 relevant studies on 5 single herbs, one extract, one receptor-agonist, and 8 combinations of herbs were identified focusing on the single herbs *Acorus calamus rhizoma*, *Cannabis sativa fructus*, *Chamomilla matricaria*, *Ginkgo biloba*, *Salvia officinalis*, Sweet bee venom, *Fritillaria cirrhosae bulbosus*, and the herbal combinations Bu Yang Huan Wu, modified Bu Yang Huan Wu plus Liuwei Di Huang, modified Chai Hu Long Gu Mu Li Wan, Geranii herba plus *Aconiti lateralis praeparata radix*, Niu Che Sen Qi Wan (Goshajinkigan), Gui Zhi Jia Shu Fu Tang (Keishikajutsuto), Huang Qi Wu Wu Tang (Ogikeishigomotsuto), and Shao Yao Gan Cao Tang (Shakuyakukanzoto). The knowledge of mechanism of action is still limited, the quality of clinical trials needs further improvement, and studies have not yielded enough evidence to establish a standard practice, but a lot of promising substances have been identified. While CIPN has multiple mechanisms of neuronal degeneration, a combination of herbs or substances might deal with multiple targets for the aim of neuroprotection or neuroregeneration in CIPN.

**The medical necessity for medicinal cannabis:
prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care**

Bar-Sela G1, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E.

Division of Oncology, Integrated Oncology and Palliative Care Unit, Rambam Health Care Campus, 31096 Haifa, Israel
Faculty of Medicine, Technion-Israel Institute of Technology, 31096 Haifa, Israel

Full text with 19 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3730175/>

Cancer patients using cannabis report better influence from the plant extract than from synthetic products. However, almost all the research conducted to date has been performed with synthetic products. We followed patients with a medicinal cannabis license to evaluate the advantages and side effects of using cannabis by cancer patients. Methods. The study included two interviews based on questionnaires regarding symptoms and side effects, the first held on the day the license was issued and the second 6-8 weeks later. Cancer symptoms and cannabis side effects were documented on scales from 0 to 4 following the CTCAE. The distress thermometer was used also.

Of the 211 patients who had a first interview, only 131 had the second interview, 25 of whom stopped treatment after less than a week. All cancer or anticancer treatment-related symptoms showed significant improvement ($P < 0.001$). No significant side effects except for memory lessening in patients with prolonged cannabis use ($P = 0.002$) were noted.

The positive effects of cannabis on various cancer-related symptoms are tempered by reliance on self-reporting for many of the variables. Although studies with a control group are missing, the improvement in symptoms should push the use of cannabis in palliative treatment of oncology patients.

Reproduction • July 2013

The role of endocannabinoids in pregnancy

Chan HW1, McKirdy NC, Peiris HN, Rice GE, Mitchell MD.

1. Royal Brisbane and Women's Hospital Campus, University of Queensland Centre for Clinical Research, The University of Queensland, Building 71/918, Herston, Queensland 4029, Australia

Full text, PDF, with 61 references

<http://www.reproduction-online.org/content/146/3/R101.full.pdf>

Endocannabinoids are a family of lipid signalling molecules. As with prostaglandins (PGs), endocannabinoids are derived from polyunsaturated fatty acids and affect cell function via receptor-mediated mechanisms. They also bind to PG receptors, although at a lower affinity. The endocannabinoid network is regulated in pregnancy from embryo development to labour onset. Even small changes in endocannabinoid exposure can retard embryo development and affect implantation success. There is now compelling evidence that aberrant expression of factors involved in the endocannabinoid pathway in the placenta and circulating lymphocytes results in spontaneous miscarriage and poor pregnancy outcomes. It is likely that competition between endocannabinoids, PGs and other similar lipids ultimately determines how phospholipid/fatty acid substrates are metabolised and, thus, the balance between the uterotonic and tocolytic activities. We, therefore, hypothesise that endocannabinoid profiles may be used as a biomarker to predict and/or identify spontaneous labour onset.

Experimental Neurology • June 2013

Marijuana, endocannabinoids, and epilepsy: potential and challenges for improved therapeutic intervention

Hofmann ME1, Frazier CJ.

Department of Pharmacodynamics, College of Pharmacy, University of Florida, USA

Full text with 127 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3332149/>

Phytocannabinoids isolated from the cannabis plant have broad potential in medicine that has been well recognized for many centuries.

It is presumed that these lipid soluble signaling molecules exert their effects in both the central and peripheral nervous system in large part through direct interaction with metabotropic cannabinoid receptors. These same receptors are also targeted by a variety of endogenous cannabinoids including 2-arachidonoyl glycerol and anandamide. Significant effort over the last decade has produced an enormous advance in our understanding of both the cellular and the synaptic physiology of endogenous lipid signaling systems. This increase in knowledge has left us better prepared to carefully evaluate the potential for both natural and synthetic cannabinoids in the treatment of a variety of neurological disorders. In the case of epilepsy, long standing interest in therapeutic approaches that target endogenous cannabinoid signaling systems are, for the most part, not well justified by available clinical data from human epileptics. Nevertheless, basic science experiments have clearly indicated a key role for endogenous cannabinoid signaling systems in moment to moment regulation of neuronal excitability. Further it has become clear that these systems can both alter and be altered by epileptiform activity in a wide range of in vitro and in vivo models of epilepsy.

Collectively these observations suggest clear potential for effective therapeutic modulation of endogenous cannabinoid signaling systems in the treatment of human epilepsy, and in fact, further highlight key obstacles that would need to be addressed to reach that goal.

Annals Of The American Thoracic Society • June 2013

Effects of marijuana smoking on the lung

By D.P. Tashkin

Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California 90095, USA
dtashkin@mednet.ucla.edu

<http://www.ncbi.nlm.nih.gov/pubmed/23802821>

Regular smoking of marijuana by itself causes visible and microscopic injury to the large airways that is consistently associated with an increased likelihood of symptoms of chronic bronchitis that subside after cessation of use. On the other hand, habitual use of marijuana alone does not appear to lead to significant abnormalities in lung function when assessed either cross-sectionally or longitudinally, except for possible increases in lung volumes and modest increases in airway resistance of unclear clinical significance. Therefore, no clear link to chronic obstructive pulmonary disease has been established. Although marijuana smoke contains a number of carcinogens and cocarcinogens, findings from a limited number of well-designed epidemiological studies do not suggest an increased risk for the development of either lung or upper airway cancer from light or moderate use, although evidence is mixed concerning possible carcinogenic risks of heavy, long-term use. Although regular marijuana smoking leads to bronchial epithelial ciliary loss and impairs the microbicidal function of alveolar macrophages, evidence is inconclusive regarding possible associated risks for lower respiratory tract infection. Several case reports have implicated marijuana smoking as an etiologic factor in pneumothorax/pneumomediastinum and bullous lung disease, although evidence of a possible causal link from epidemiologic studies is lacking. In summary, the accumulated weight of evidence implies far lower risks for pulmonary complications of even regular heavy use of marijuana compared with the grave pulmonary consequences of tobacco.

Neuropsychological Review • June 2013

Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences

Crane NA1, Schuster RM, Fusar-Poli P, Gonzalez R.

Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Full text with 220 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3593817/>

Decades of research have examined the effects of cannabis on neurocognition. Recent advances in this field provide us with a better understanding of how cannabis use influences neurocognition both acutely (during intoxication) and non-acutely (after acute effects subside). Evidence of problems with episodic memory is one of the most consistent findings reported; however, several other neurocognitive domains appear to be adversely affected by cannabis use under various conditions. There is significant variability in findings across studies, thus a discussion of potential moderators is increasingly relevant. The purpose of this review was to 1) provide an update on research of cannabis' acute and non-acute effects on neurocognition, with a focus on findings since 2007 and 2) suggest and discuss how neurodevelopmental issues and sex differences may influence cannabis effects on neurocognition. Finally we discuss how future investigations may lead to better understanding of the complex interplay among cannabis, stages of neurodevelopment, and sex on neurocognitive functioning.

Nutricion Hospitalaria • May 2013

Changes on metabolic parameters induced by acute cannabinoid administration (CBD, THC) in a rat experimental model of nutritional vitamin A deficiency

El Amrani L1, Porres JM, Merzouki A, Louktibi A, Aranda P, López-Jurado M, Urbano G.

Department of Physiology, School of Pharmacy, Institute of Nutrition and Food Technology, University of Granada, Granada, Spain

Full text, PDF, with 49 references

<http://www.nutricionhospitalaria.com/pdf/6430.pdf>

Vitamin A deficiency can result from malnutrition, malabsorption of vitamin A, impaired vitamin metabolism associated with liver disease, or chronic debilitating diseases like HIV infection or cancer.

Cannabis administration has been described as a palliative symptom management therapy in such pathological stages. Therefore, this research aimed to study the effects of acute administration of cannabidiol (CBD) or tetrahydrocannabinol (THC) on the levels of retinol in plasma and in the liver, and biochemical parameters related to lipid and glucose metabolism (cholesterolaemia, triglyceridemia and glycemia) in a rat experimental model of vitamin A deficiency.

Under our experimental conditions, the reported effects of cannabinoid administration on certain signs of nutritional vitamin A deficiency appeared to be mediated through mechanisms other than changes in retinol metabolism or its mobilization after the acute administration of such compounds.

Medicinal Cannabis and Painful Sensory Neuropathy

By Igor Grant, MD

Full text with 12 references

<http://journalofethics.ama-assn.org/2013/05/oped1-1305.html>

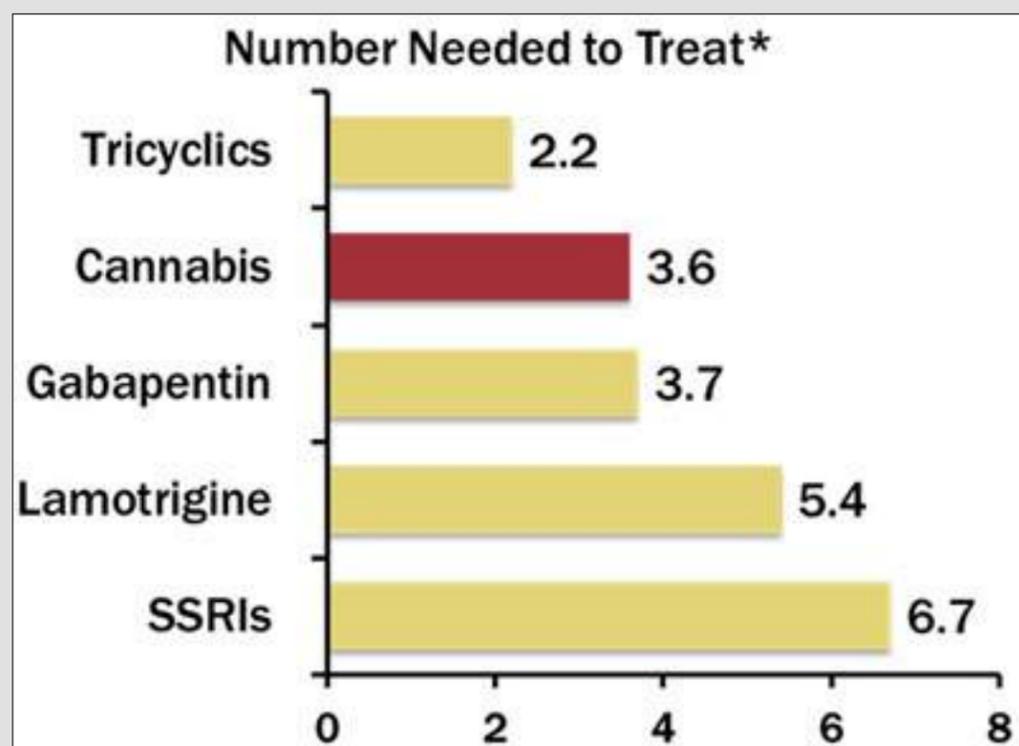


Figure 1. Common analgesics for neuropathic pain, *to achieve a 30% reduction in pain.

Painful peripheral neuropathy comprises multiple symptoms that can severely erode quality of life. These include allodynia (pain evoked by light stimuli that are not normally pain-evoking) and various abnormal sensations termed dysesthesias (e.g., electric shock sensations, “pins and needles,” sensations of coldness or heat, numbness, and other types of uncomfortable and painful sensations). Common causes of peripheral neuropathy include diabetes, HIV/AIDS, spinal cord injuries, multiple sclerosis, and certain drugs and toxins. Commonly prescribed treatments come from drugs of the tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressant classes, anticonvulsants, opioids, and certain topical agents. Many patients receive only partial benefit from such treatments, and some either do not benefit or cannot tolerate these medications. The need for additional treatment modalities is evident.

Animal studies and anecdotal human evidence have for some time pointed to the possibility that cannabis may be effective in the treatment of painful peripheral neuropathy [1]. Recently, the Center for Medicinal Cannabis Research (CMCR) at the University of California [2] completed five placebo-controlled phase II clinical trials with smoked or inhaled cannabis [3-7]. Another study reported from Canada [8]. Patients includ-

ed people with HIV neuropathy and other neuropathic conditions, and one study focused on a human model of neuropathic pain. Overall, the efficacy of cannabis was comparable to that of traditional agents, somewhat less than that of the tricyclics, but better than SSRIs and anticonvulsants, and comparable to gabapentin (see figure 1).

Cannabidiol in inflammatory bowel diseases: a brief overview

Esposito G1, Filippis DD, Cirillo C, Iuvone T, Capoccia E, Scuderi C, Steardo A, Cuomo R, Steardo L.

1. Department of Physiology and Pharmacology Vittorio Erspamer, Faculty of Pharmacy and Medicine, Sapienza University of Rome, Italy
giuseppe.esposito@uniroma1.it

<http://www.ncbi.nlm.nih.gov/pubmed/22815234>

This minireview highlights the importance of cannabidiol (CBD) as a promising drug for the therapy of inflammatory bowel diseases (IBD). Actual pharmacological treatments for IBD should be enlarged toward the search for low-toxicity and low-cost drugs that may be given alone or in combination with the conventional anti-IBD drugs to increase their efficacy in the therapy of relapsing forms of colitis. In the past, Cannabis preparations have been considered new promising pharmacological tools in view of their anti-inflammatory role in IBD as well as other gut disturbances. However, their use in the clinical therapy has been strongly limited by their psychotropic effects. CBD is a very promising compound since it shares the typical cannabinoid beneficial effects on gut lacking any psychotropic effects. For years, its activity has been enigmatic for gastroenterologists and pharmacologists, but now it is evident that this compound may interact at extra-cannabinoid system receptor sites, such as peroxisome proliferator-activated receptor-gamma. This strategic interaction makes CBD as a potential candidate for the development of a new class of anti-IBD drugs.

Cannabis use and impairment of respiratory function

Underner M1, Urban T, Perriot J, Peiffer G, Meurice JC.

1. Unité de tabacologie, service de pneumologie, centre de lutte antituberculeuse CLAT 86, pavillon René-Beauchant, 86021 Poitiers cedex, France
m.underner@chu-poitiers.fr

<http://www.ncbi.nlm.nih.gov/pubmed/23664286>

Cannabis is the most commonly smoked illicit substance in many countries including France. It can be smoked alone in plant form (marijuana) but in our country it is mainly smoked in the form of cannabis resin mixed with tobacco. The technique of inhaling cannabis differs from that of tobacco, increasing the time that the smoke spends in contact with the bronchial mucosal and its impact on respiratory function. One cigarette composed of cannabis and tobacco is much more harmful than a cigarette containing only tobacco. In cannabis smokers there is an increased incidence of respiratory symptoms and episodes of acute bronchitis. Cannabis produces a rapid bronchodilator effect; chronic use provokes a reduction in specific conductance and increase in airways resistance. Studies on the decline of Forced Expiratory Volume are discordant. Cannabis smoke and tetrahydrocannabinol irritate the bronchial tree. They bring about histological signs of airways inflammation and alter the fungicidal and antibacterial activity of alveolar macrophages. Inhalation of cannabis smoke is a risk factor for lung cancer. Stopping smoking cannabis will bring about important benefits for lung function. This should encourage clinicians to offer patients support in quitting smoking.

The impact of cannabis use on age of onset and clinical characteristics in first-episode psychotic patients Data from the Psychosis Incident Cohort Outcome Study (PICOS)

Tosato S, Lasalvia A, Bonetto C, Mazzoncini R, Cristofalo D, De Santi K, Bertani M, Bissoli S, Lazzarotto L, Marrella G, Lamonaca D, Riolo R, Gardellin F, Urbani A, Tansella M, Ruggeri M; PICOS-VENETO Group.
Collaborators (144)

<http://www.ncbi.nlm.nih.gov/pubmed/23290558>

Cannabis use is frequent among first-episode psychosis (FEP) patients and has been associated with several clinical features. This study aimed in an FEP sample to determine whether cannabis use is associated with (1) a higher level of positive symptoms, a lower level of depression and a better premorbid adjustment, (2) an earlier age of onset, and a better premorbid IQ. The study was conducted within the framework of the Psychosis Incident Cohort Outcome Study (PICOS), a multisite collaborative research on FEP patients who attended the psychiatric services in Veneto Region, Italy. Standardized instruments were used to collect sociodemographic, clinical, and drug use data. A total of 555 FEP patients met the inclusion criteria, 517 of whom received an ICD-10 diagnosis of psychosis; 397 (55% males; mean age: 32 yrs \pm 9.5) were assessed. Out of these, 311 patients agreed to be interviewed on drug and alcohol misuse; 20.3% was positive for drug misuse: cannabis (19.0%), cocaine (3.9%), and hallucinogens (3.9%). Cannabis use was not associated with a higher level of positive symptoms, but correlated with less severe depressive symptoms. No relationship was observed between premorbid adjustment or IQ and cannabis use. FEP patients who used cannabis had an earlier age of onset than abstinent patients, even after adjusting for gender and diagnosis. Our results suggest a possible causal role of cannabis in triggering psychosis in certain vulnerable subjects. Particular attention must be paid to this behaviour, because reducing cannabis use can delay or prevent some cases of psychosis.

Proceedings Of The National Academy Of Science USA • March 2013

Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status

By O. Rogeberg

The Ragnar Frisch Centre for Economic Research, N-0349 Oslo, Norway
ole.rogeberg@frisch.uio.no

Full text with 29 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3600466/>

Does cannabis use have substantial and permanent effects on neuropsychological functioning? Renewed and intense attention to the issue has followed recent research on the Dunedin cohort, which found a positive association between, on the one hand, adolescent-onset cannabis use and dependence and, on the other hand, a decline in IQ from childhood to adulthood [Meier et al. (2012) Proc Natl Acad Sci USA 109(40):E2657-E2664]. The association is given a causal interpretation by the authors, but existing research suggests an alternative confounding model based on time-varying effects of socioeconomic status on IQ. A simulation of the confounding model reproduces the reported associations from the Dunedin cohort, suggesting that the causal effects estimated in Meier et al. are likely to be overestimates, and that the true effect could be zero. Further analyses of the Dunedin cohort are proposed to distinguish between the competing interpretations. Although it would be too strong to say that the results have been discredited, the methodology is flawed and the causal inference drawn from the results premature.

Expert Reviews In Neurotherapy • February 2013

A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany

By P. Flachenecker

Neurological Rehabilitation Center Quellenhof, Kuranlagenallee 2, 75323 Bad Wildbad, Germany
peter.flachenecker@sana.de

<http://www.ncbi.nlm.nih.gov/pubmed/23369055>

Sativex® (GW Pharmaceuticals PLC, Porton Down, UK; Laboratorios Almirall, SA, Barcelona, Spain), a cannabinoid oromucosal spray containing a 1:1 ratio of 9- δ -tetrahydrocannabinol and cannabidiol, has been licensed in Germany since July 2011 as add-on therapy for moderate-to-severe multiple sclerosis (MS) treatment-resistant spasticity symptoms. The 'MOVE 2' study evaluated clinical outcomes, treatment satisfaction, quality of life (QoL) and provision of care in MS patients with spasticity receiving Sativex in everyday clinical practice. Data from 300 patients were collected from 42 specialized MS centers across Germany and were available for this analysis. Assessments, including the MS spasticity 0-10 numerical rating scale, modified Ashworth scale, patients' and physicians' clinical impressions, and QoL scales were rated at baseline and at 1 and 3 months after starting treatment with Sativex. Sativex provided relief of MS-related spasticity in the majority of patients who were previously resistant to treatment. In addition, clear improvements were noted in MS spasticity-associated symptoms (e.g., sleep quality, bladder function and mobility), activities of daily living and QoL. Sativex was generally well tolerated. The majority of patients (84%) reported no adverse events, and there was only a limited risk of serious adverse reactions. Furthermore, based on data from Sativex clinical trials, a Markov model-based analysis has shown that Sativex is a cost-effective treatment option for patients with MS spasticity in Germany.

Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings

Albert Batalla,^{1,2,3} Sagnik Bhattacharyya,⁴ Murat Yücel,³ Paolo Fusar-Poli,⁴ Jose Alexandre Crippa,^{5,6}
Santiago Nogué,⁷ Marta Torrens,^{8,9} Jesús Pujol,¹⁰ Magí Farré,^{8,9} and Rocio Martin-Santos^{1,2,6,*}

1. Psychiatry, Institute of Neurosciences, Hospital Clínic, IDIBAPS, CIBERSAM, Barcelona, Spain
2. Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Barcelona, Spain
3. Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, Victoria, Australia
4. Department of Psychosis Studies, King's College London, Institute of Psychiatry, London, UK
5. Neuroscience and Cognitive Behavior Department, University of Sao Paulo, Ribeirao Preto, Brazil
6. National Science and Technology Institute for Translational Medicine (INCT-TM, CNPq), Ribeirao Preto, Brazil
7. Clinical Toxicology Unit, Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain
8. Neuroscience Program, Pharmacology Unit and Drug Addiction Unit, IMIM-INAD-Parc de Salut Mar, Autonomous University of Barcelona, Barcelona, Spain
9. Red de Trastornos Adictivos (RETIC), IMIM-INAD-Parc de Salut Mar, Barcelona, Spain
10. Institut d'Alta Tecnologia-PRBB, CRC Mar, Hospital del Mar, Barcelona, Spain
Peking University, China

Full text with 193 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563634/>

The growing concern about cannabis use, the most commonly used illicit drug worldwide, has led to a significant increase in the number of human studies using neuroimaging techniques to determine the effect of cannabis on brain structure and function. We conducted a systematic review to assess the evidence of the impact of chronic cannabis use on brain structure and function in adults and adolescents.

One hundred and forty-two studies were identified, of which 43 met the established criteria. Eight studies were in adolescent population. Neuroimaging studies provide evidence of morphological brain alterations in both population groups, particularly in the medial temporal and frontal cortices, as well as the cerebellum. These effects may be related to the amount of cannabis exposure. Functional neuroimaging studies suggest different patterns of resting global and brain activity during the performance of several cognitive tasks both in adolescents and adults, which may indicate compensatory effects in response to chronic cannabis exposure.

Chronic cannabis use may alter brain structure and function in adult and adolescent population. Further studies should consider the use of convergent methodology, prospective large samples involving adolescent to adulthood subjects, and data-sharing initiatives.

Is the cardiovascular system a therapeutic target for cannabidiol?

Stanley CP1, Hind WH, O'Sullivan SE.

1. School of Graduate Entry Medicine & Health, Royal Derby Hospital, University of Nottingham, DE22 3DT, UK

Full text with 89 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579247/>

Cannabidiol (CBD) has beneficial effects in disorders as wide ranging as diabetes, Huntington's disease, cancer and colitis. Accumulating evidence now also suggests that CBD is beneficial in the cardiovascular system. CBD has direct actions on isolated arteries, causing both acute and time-dependent vasorelaxation. In vitro incubation with CBD enhances the vasorelaxant responses in animal models of impaired endothelium-dependent vasorelaxation. CBD protects against the vascular damage caused by a high glucose environment, inflammation or the induction of type 2 diabetes in animal models and reduces the vascular hyperpermeability associated with such environments. A common theme throughout these studies is the anti-inflammatory and anti-oxidant effect of CBD. In the heart, in vivo CBD treatment protects against ischaemia-reperfusion damage and against cardiomyopathy associated with diabetes. Similarly, in a different model of ischaemia-reperfusion, CBD has been shown to reduce infarct size and increase blood flow in animal models of stroke, sensitive to 5HT(1A) receptor antagonism. Although acute or chronic CBD treatment seems to have little effect on haemodynamics, CBD reduces the cardiovascular response to models of stress, applied either systemically or intracranially, inhibited by a 5HT(1A) receptor antagonist. In blood, CBD influences the survival and death of white blood cells, white blood cell migration and platelet aggregation. Taken together, these preclinical data appear to support a positive role for CBD treatment in the heart, and in peripheral and cerebral vasculature. However, further work is required to strengthen this hypothesis, establish mechanisms of action and whether similar responses to CBD would be observed in humans.

Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings

Albert Batalla, Rocio Martin-Santos
Psychiatry, Institute of Neurosciences, Hospital Clínic, IDIBAPS, CIBERSAM, Barcelona, Spain
Albert Batalla, Rocio Martin-Santos
Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Barcelona, Spain
Albert Batalla, Murat Yücel
Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, Victoria, Australia
Sagnik Bhattacharyya, Paolo Fusar-Poli
Department of Psychosis Studies, King's College London, Institute of Psychiatry, London, United Kingdom
Jose Alexandre Crippa
Neuroscience and Cognitive Behavior Department, University of Sao Paulo, Ribeirao Preto, Brazil
Jose Alexandre Crippa, Rocio Martin-Santos
National Science and Technology Institute for Translational Medicine (INCT-TM, CNPq), Ribeirao Preto, Brazil
Santiago Nogué
Clinical Toxicology Unit, Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain
Marta Torrens, Magí Farré
Neuroscience Program, Pharmacology Unit and Drug Addiction Unit, IMIM-INAD-Parc de Salut Mar, Autonomous University of Barcelona, Barcelona, Spain
Marta Torrens, Magí Farré
Red de Trastornos Adictivos (RETIC), IMIM-INAD-Parc de Salut Mar, Barcelona, Spain
Jesús Pujol
Institut d'Alta Tecnologia-PRBB, CRC Mar, Hospital del Mar, Barcelona, Spain

Full text with 193 references

Journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0055821

The growing concern about cannabis use, the most commonly used illicit drug worldwide, has led to a significant increase in the number of human studies using neuroimaging techniques to determine the effect of cannabis on brain structure and function. We conducted a systematic review to assess the evidence of the impact of chronic cannabis use on brain structure and function in adults and adolescents.

Papers published until August 2012 were included from EMBASE, Medline, PubMed and LILACS databases following a comprehensive search strategy and pre-determined set of criteria for article selection. Only neuroimaging studies involving chronic cannabis users with a matched control group were considered. One hundred and forty-two studies were identified, of which 43 met the established criteria. Eight studies were in adolescent population. Neuroimaging studies provide evidence of morphological brain alterations in both population groups, particularly in the medial temporal and frontal cortices, as well as the cerebellum. These effects may be related to the amount of cannabis exposure. Functional neuroimaging studies suggest different patterns of resting global and brain activity during the performance of several cognitive tasks both in adolescents and adults, which may indicate compensatory effects in response to chronic cannabis exposure. However, the results pointed out methodological limitations of the work conducted to date and considerable heterogeneity in the findings.

Chronic cannabis use may alter brain structure and function in adult and adolescent population. Further studies should consider the use of convergent methodology, prospective large samples involving adolescent to adulthood subjects, and data-sharing initiatives.

The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood

Degenhardt L1, Coffey C, Romaniuk H, Swift W, Carlin JB, Hall WD, Patton GC.

1. National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia
l.degenhardt@unsw.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/22775447>

Debate continues about whether the association between cannabis use in adolescence and common mental disorders is causal. Most reports have focused on associations in adolescence, with few studies extending into adulthood. We examine the association from adolescence until the age of 29 years in a representative prospective cohort of young Australians.

There were no consistent associations between adolescent cannabis use and depression at age 29 years. Daily cannabis use was associated with anxiety disorder at 29 years [adjusted OR 2.5, 95% confidence interval (CI):< 1.2-5.2], as was cannabis dependence (adjusted OR 2.2, 95% CI: 1.1-4.4). Among weekly+ adolescent cannabis users, those who continued to use cannabis use daily at 29 years remained at significantly increased odds of anxiety disorder (adjusted OR 3.2, 95% CI: 1.1-9.2).

Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety, but not depressive disorder, in adolescence and late young adulthood, even among regular users who then cease using the drug. It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population.



CANNABIS • 2012 PEER REVIEW

Epilepsy Behavior • December 2012

Seizure exacerbation in two patients with focal epilepsy following marijuana cessation

Hegde M1, Santos-Sanchez C, Hess CP, Kabir AA, Garcia PA.

Epilepsy Center, Department of Neurology, University of California, San Francisco, San Francisco, CA 94143-0138, USA
manu.hegde@ucsf.edu

<http://www.ncbi.nlm.nih.gov/pubmed/23159379>

While animal models of epilepsy suggest that exogenous cannabinoids may have anticonvulsant properties, scant evidence exists for these compounds' efficacy in humans. Here, we report on two patients whose focal epilepsy was nearly controlled through regular outpatient marijuana use. Both stopped marijuana upon admission to our epilepsy monitoring unit (EMU) and developed a dramatic increase in seizure frequency documented by video-EEG telemetry. These seizures occurred in the absence of other provocative procedures, including changes to anticonvulsant medications. We review these cases and discuss mechanisms for the potentially anticonvulsant properties of cannabis, based on a review of the literature.

Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities

By R.G. Pertwee

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK
rgp@abdn.ac.uk

Full text with 129 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481523/>

Human tissues express cannabinoid CB(1) and CB(2) receptors that can be activated by endogenously released 'endocannabinoids' or exogenously administered compounds in a manner that reduces the symptoms or opposes the underlying causes of several disorders in need of effective therapy. Three medicines that activate cannabinoid CB(1)/CB(2) receptors are now in the clinic: Cesamet (nabilone), Marinol (dronabinol; $\Delta(9)$ -tetrahydrocannabinol ($\Delta(9)$ -THC)) and Sativex ($\Delta(9)$ -THC with cannabidiol). These can be prescribed for the amelioration of chemotherapy-induced nausea and vomiting (Cesamet and Marinol), stimulation of appetite (Marinol) and symptomatic relief of cancer pain and/or management of neuropathic pain and spasticity in adults with multiple sclerosis (Sativex). This review mentions several possible additional therapeutic targets for cannabinoid receptor agonists. These include other kinds of pain, epilepsy, anxiety, depression, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, stroke, cancer, drug dependence, glaucoma, autoimmune uveitis, osteoporosis, sepsis, and hepatic, renal, intestinal and cardiovascular disorders. It also describes potential strategies for improving the efficacy and/or benefit-to-risk ratio of these agonists in the clinic. These are strategies that involve (i) targeting cannabinoid receptors located outside the blood-brain barrier, (ii) targeting cannabinoid receptors expressed by a particular tissue, (iii) targeting upregulated cannabinoid receptors, (iv) selectively targeting cannabinoid CB(2) receptors, and/or (v) adjunctive 'multi-targeting'.

Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders

Campos AC1, Moreira FA, Gomes FV, Del Bel EA, Guimarães FS.

1. Group of Neuroimmunology, Laboratory of Immunopharmacology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Full text with 135 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481531/>

Cannabidiol (CBD) is a major phytocannabinoid present in the *Cannabis sativa* plant. It lacks the psychotomimetic and other psychotropic effects that the main plant compound $\Delta(9)$ -tetrahydrocannabinol (THC) being able, on the contrary, to antagonize these effects. This property, together with its safety profile, was an initial stimulus for the investigation of CBD pharmacological properties. It is now clear that CBD has therapeutic potential over a wide range of non-psychiatric and psychiatric disorders such as anxiety, depression and psychosis. Although the pharmacological effects of CBD in different biological systems have been extensively investigated by *in vitro* studies, the mechanisms responsible for its therapeutic potential are still not clear. Here, we review recent *in vivo* studies indicating that these mechanisms are not unitary but rather depend on the behavioural response being measured. Acute anxiolytic and antidepressant-like effects seem to rely mainly on facilitation of 5-HT_{1A}-mediated neurotransmission in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex. Other effects, such as anti-compulsive, increased extinction and impaired reconsolidation of aversive memories, and facilitation of adult hippocampal neurogenesis could depend on potentiation of anandamide-mediated neurotransmission. Finally, activation of TRPV1 channels may help us to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD. Considering its safety profile and wide range of therapeutic potential, however, further studies are needed to investigate the involvement of other possible mechanisms (e.g. inhibition of adenosine uptake, inverse agonism at CB₂ receptor, CB₁ receptor antagonism, GPR55 antagonism, PPAR γ receptors agonism, intracellular (Ca²⁺) increase, etc.), on CBD behavioural effects.

First systematic evaluation of the potency of *Cannabis sativa* plants grown in Albania

Bruci Z1, Papoutsis I, Athanaselis S, Nikolaou P, Pazari E, Spiliopoulou C, Vyshka G.

Department of Forensic Medicine and Toxicology, School of Medicine, University of Tirana, Albania
zbruci@yahoo.com

<http://www.ncbi.nlm.nih.gov/pubmed/22608266>

Cannabis products (marijuana, hashish, cannabis oil) are the most frequently abused illegal substances worldwide. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive component of *Cannabis sativa* plant, whereas cannabidiol (CBD) and cannabinol (CBN) are other major but not psychoactive constituents. Many studies have already been carried out on these compounds and chemical research was encouraged due to the legal implications concerning the misuse of marijuana. The aim of this study was to determine THC, CBD and CBN in a significant number of cannabis samples of Albanian origin, where cannabis is the most frequently used drug of abuse, in order to evaluate and classify them according to their cannabinoid composition. A GC-MS method was used, in order to assay cannabinoid content of hemp samples harvested at different maturation degree levels during the summer months and grown in different areas of Albania. This method can also be used for the determination of plant phenotype, the evaluation of psychoactive potency and the control of material quality. The highest cannabinoid concentrations were found in the flowers of cannabis. The THC concentrations in different locations of Albania ranged from 1.07 to 12.13%. The influence of environmental conditions on cannabinoid content is discussed. The cannabinoid content of cannabis plants were used for their profiling, and it was used for their classification, according to their geographical origin. The determined concentrations justify the fact that Albania is an area where cannabis is extensively cultivated for illegal purposes.

Proceedings Of The National Academy Of Science USA • October 2012

Persistent cannabis users show neuropsychological decline from childhood to midlife

Meier MH¹, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE.

Department of Psychology and Neuroscience, Duke University, Durham, NC 27708, USA
madeline.meier@duke.edu

Full text with 54 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3479587/>

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users

Schacht JP1, Hutchison KE, Filbey FM.

1. Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA
schacht@musc.edu

Full text with 51 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442352/>

Heavy cannabis users display smaller amygdalae and hippocampi than controls, and genetic variation accounts for a large proportion of variance in liability to cannabis dependence (CD). A single nucleotide polymorphism in the cannabis receptor-1 gene (CNR1), rs2023239, has been associated with CD diagnosis and intermediate phenotypes, including abstinence-induced withdrawal, cue-elicited craving, and parahippocampal activation to cannabis cues. This study compared hippocampal and amygdalar volumes (potential CD intermediate phenotypes) between heavy cannabis users and healthy controls, and analyzed interactions between group, rs2023239 variation, and the volumes of these structures. Ninety-four heavy cannabis users participated, of whom 37 (14 men, 23 women; mean age=27.8) were matched to 37 healthy controls (14 men, 23 women; mean age=27.3) for case-control analyses. Controlling for total intracranial volume and other confounding variables, matched cannabis users had smaller bilateral hippocampi (left, $p=0.002$; right, $p=0.001$) and left amygdalae ($p=0.01$) than controls. When genotype was considered in the case-control analyses, there was a group by genotype interaction, such that the rs2023239 G allele predicted lower volume of bilateral hippocampi among cannabis users relative to controls (both $p<0.001$). This interaction persisted when all 94 cannabis users were compared to controls. There were no group by genotype interactions on amygdalar volume. These data replicate previous findings of reduced hippocampal and amygdalar volume among heavy cannabis users, and suggest that CNR1 rs2023239 variation may predispose smaller hippocampal volume after heavy cannabis use. This association should be tested in future studies of brain volume differences in CD.

The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity

Alhouayek M1, Muccioli GG.

1. Bioanalysis and Pharmacology of Bioactive Lipids Research Group, Louvain Drug Research Institute
Université catholique de Louvain, Av. E. Mounier, 72, B1.72.01, 1200 Bruxelles, Belgium

<http://www.ncbi.nlm.nih.gov/pubmed/22917662>

Crohn's disease and ulcerative colitis are two major forms of inflammatory bowel diseases (IBD), which are chronic inflammatory disorders of the gastrointestinal tract. These pathologies are currently under investigation to both unravel their etiology and find novel treatments. Anandamide and 2-arachidonoylglycerol are endogenous bioactive lipids that bind to and activate the cannabinoid receptors, and together with the enzymes responsible for their biosynthesis and degradation [fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)] constitute the endocannabinoid system (ECS). The ECS is implicated in gut homeostasis, modulating gastrointestinal motility, visceral sensation, and inflammation, as well as being recently implicated in IBD pathogenesis. Numerous subsequent studies investigating the effects of cannabinoid agonists and endocannabinoid degradation inhibitors in rodent models of IBD have identified a potential therapeutic role for the ECS.

Age of onset of marijuana use and executive function

Gruber SA1, Sagar KA, Dahlgren MK, Racine M, Lukas SE.

1. Cognitive and Clinical Neuroimaging Core, Brain Imaging Center, McLean Hospital, Belmont, MA 02478, USA
gruber@mclean.harvard.edu

Full text with 50 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3345171/>

Marijuana (MJ) remains the most widely abused illicit substance in the United States, and in recent years, a decline in perceived risk of MJ use has been accompanied by a simultaneous increase in rates of use among adolescents. In this study, the authors hypothesized that chronic MJ smokers would perform cognitive tasks, specifically those that require executive function, more poorly than control subjects and that individuals who started smoking MJ regularly prior to age 16 (early onset) would have more difficulty than those who started after age 16 (late onset). Thirty-four chronic, heavy MJ smokers separated into early and late onset groups, and 28 non-MJ smoking controls completed a battery of neurocognitive measures. As hypothesized, MJ smokers performed more poorly than controls on several measures of executive function. Age of onset analyses revealed that these between-group differences were largely attributed to the early onset group, who were also shown to smoke twice as often and nearly 3 times as much MJ per week relative to the late onset smokers. Age of onset, frequency, and magnitude of MJ use were all shown to impact cognitive performance. Findings suggest that earlier MJ onset is related to poorer cognitive function and increased frequency and magnitude of MJ use relative to later MJ onset. Exposure to MJ during a period of neurodevelopmental vulnerability, such as adolescence, may result in altered brain development and enduring neuropsychological changes.

Oxford University Press - Brain A Journal Of Neurology • July 2012

Effect of long-term cannabis use on axonal fibre connectivity

Zalesky A1, Solowij N, Yücel M, Lubman DI, Takagi M, Harding IH, Lorenzetti V, Wang R, Searle K, Pantelis C, Seal M.

Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Melbourne, 3053, Australia

Full text with 74 references

<http://brain.oxfordjournals.org/content/135/7/2245.long>

Cannabis use typically begins during adolescence and early adulthood, a period when cannabinoid receptors are still abundant in white matter pathways across the brain. However, few studies to date have explored the impact of regular cannabis use on white matter structure, with no previous studies examining its impact on axonal connectivity. The aim of this study was to examine axonal fibre pathways across the brain for evidence of microstructural alterations associated with long-term cannabis use and to test whether age of regular cannabis use is associated with severity of any microstructural change. To this end, diffusion-weighted magnetic resonance imaging and brain connectivity mapping techniques were performed in 59 cannabis users with longstanding histories of heavy use and 33 matched controls. Axonal connectivity was found to be impaired in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum and commissural fibres. Radial and axial diffusivity in these pathways were associated with the age at which regular cannabis use commenced. Our findings indicate long-term cannabis use is hazardous to the white matter of the developing brain. Delaying the age at which regular use begins may minimize the severity of microstructural impairment.

Clinical Microbiological Infection • July 2012

**Crosstalk between the gut microbiota and the endocannabinoid system:
impact on the gut barrier function and the adipose tissue**

By P.D. Cani

Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Université Catholique de Louvain, Brussels, Belgium
patrice.cani@uclouvain.be

Full text, PDF, with 15 references

[http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X\(14\)60970-8/pdf](http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)60970-8/pdf)

Obesity is associated with type 2 diabetes, insulin resistance and low grade inflammation. The gut microbiota is now considered as one of the most important environmental factors impacting on host physiology and metabolism. We have recently pointed out the role of this 'organ' on the onset of insulin resistance and the low grade inflammatory tone characterizing obesity. Among the mechanisms, we have introduced the novel concept of metabolic endotoxaemia as factor triggering low grade inflammation and associated disorders. More recently, two novel mechanisms involved in the development of gut permeability and adipose tissue plasticity have been identified. Specific attention has been paid to the role of the glucagon-like peptide 2 and the endocannabinoid system. This review briefly discusses the role of prebiotics as a key tool to modulate the gut microbiota, the gut barrier function, inflammation and the insulin resistance associated with obesity.

Open Neurology Journal • July 2012

Medical marijuana: clearing away the smoke

Grant I1, Atkinson JH, Gouaux B, Wilsey B.

1. Center for Medicinal Cannabis Research; University of California, San Diego; San Diego, CA, USA

Full text, PDF, with 62 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3358713/pdf/TONEUJ-6-18.pdf>

Recent advances in understanding of the mode of action of tetrahydrocannabinol and related cannabinoid ingredients of marijuana, plus the accumulating anecdotal reports on potential medical benefits have spurred increasing research into possible medicinal uses of cannabis. Recent clinical trials with smoked and vaporized marijuana, as well as other botanical extracts indicate the likelihood that the cannabinoids can be useful in the management of neuropathic pain, spasticity due to multiple sclerosis, and possibly other indications. As with all medications, benefits and risks need to be weighed in recommending cannabis to patients. We present an algorithm that may be useful to physicians in determining whether cannabis might be recommended as a treatment in jurisdictions where such use is permitted.

Cognition and cannabis: from anecdote to advanced technology

By J.C. Brust

Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, USA
jcb2@mail.cumc.columbia.edu

Full text with 17 references

<http://brain.oxfordjournals.org/content/135/7/2004.long>

Whether the use of cannabis causes lasting cognitive or behavioural alteration has been controversial for decades. Studies addressing the problem have often been confounded by failure to account for residual acute effects or withdrawal and by failure to measure cognitive function before drug use. Investigative strategies have included neuropsychological testing, brain activation during cognitive tasks, epidemiology and identification of morphological alteration in the brains of cannabis users.

In this issue of *Brain*, Zalesky et al. (2012) apply a novel strategy—diffusion-weighted MRI and connectivity mapping—to demonstrate microstructural alterations affecting brain axonal pathways in long-term cannabis users. Without predefined regions of interest, thousands of voxel pairs were compared, and impaired axonal connectivity was identified in the fimbria of the hippocampus and the splenium of the corpus callosum. These abnormalities were greatest in subjects who began regular marijuana use during early adolescence and were present in white matter structures in which cannabinoid (CB)1 receptor density is maximal in utero and during childhood. The findings are consistent with the endocannabinoid system playing a key role in brain development, and they provide a plausible explanation for lasting cognitive impairment after disruption of the endocannabinoid system during childhood or adolescence.

Numerous reports have described neuropsychological testing in cannabis users. In a study in which IQ scores were measured at age 9–12 years and again at age 17–20 years, a decline was observed in heavy users compared with former heavy users, but other than ‘no use of marijuana on the day of testing’, there was no defined period of pre-test abstinence (Fried et al., 2002). A study of high school seniors matched for IQ in the fourth grade found impaired memory, mathematical skills and verbal expression in heavy users compared with light users, but testing was performed only 17 h after last use (Block and Ghonheim, 1993). More convincingly, a study of adolescents and young adults matched for IQ and age-identified negative effects of heavy cannabis use on memory, executive function and psychomotor speed after 28 days of abstinence (Bolla et al., 2002).

Similarly confounded are studies using PET or functional MRI to measure brain activation during cognitive testing. Tasks involving attention, recent memory, working memory and motor performance have demonstrated abnormal patterns of activation in prefrontal cortex, hippocampus, basal ganglia or cerebellum after abstinence periods of 24–36 h (Chang et al., 2006). A study of inhibition (the Stroop task) found activation to be abnormally decreased or increased (perhaps reflecting impaired efficiency) in prefrontal and limbic areas after 25 days of abstinence (Eldreth et al., 2004). A study of decision making (the Iowa

Gambling Task) found reduced prefrontal activation after 25 days of abstinence (Bolla et al., 2005). Some studies report normal cognitive task performance despite abnormal activation patterns (Jager et al., 2007).

Epidemiological studies offer evidence that cannabis use is a significant risk factor for schizophrenia. A review of such studies concluded that the risk exists independently of several confounders (LeBec et al., 2009). In untreated schizophrenic patients, levels of the endocannabinoid anandamide are increased in CSF (Leweke et al., 1999), and CB1 receptors are upregulated in the anterior cingulate cortex (Zavitsanou et al., 2004). It has been proposed that excessive endocannabinoids (or exogenous delta-9-tetrahydrocannabinol, the principal psychoactive compound in cannabis) disrupt limbic and prefrontal dopaminergic activity, eventually triggering schizophrenic symptoms in genetically or environmentally predisposed individuals (Fernandez-Espejo et al., 2009).

Attempts to identify the effects of in utero exposure to cannabis have had to account for the effects of inadequate prenatal care and exposure to other drugs, including tobacco and ethanol. Several studies have described impaired executive function persisting into late adolescence (Smith et al., 2006). Endocannabinoids play an important role in foetal brain development, with a different distribution of CB1 receptors compared with the adult brain (Harkeny et al., 2007).

Abnormalities on neuropsychological testing and functional MRI acti-

vation are consistent with imaging studies demonstrating morphological changes in cannabis users. Some reports have described reduced grey matter in limbic areas (Lorenzetti et al., 2010; Cousijn et al., 2012), and diffusion tensor imaging has identified reduced fractional anisotropy in white matter structures (Ashtari et al., 2009).

The observations by Zelesky et al. provide persuasive evidence of clinically relevant morphological brain abnormalities in cannabis users, especially in view of the absence of predetermined regions of interest, the location of abnormalities in regions that contain abundant cannabinoid receptors during brain development and the identification of the abnormalities in adolescent users, whose brains are continuing to develop. Compared with non-users, users had 'lower Global Assessment of Functioning scores' considered 'typical of the general population of cannabis users', but formal neuropsychological testing was not performed, and so it remains to be seen whether cognitive impairment parallels the neuropathology. The authors acknowledge that 'the precise microstructural underpinnings' of their observations are not well understood, and they do not discount the possibility that abstention from cannabis might lead to recovery from axonal injury. They emphasize, however, that their findings reflect 'structural/morphological... abnormalities not functional abnormalities'. Such lesions would be difficult to explain as residual acute effects or withdrawal or as anatomical variations predating cannabis use. Advanced technology thus adds to ever accumulating evidence that cannabis use by children and adolescents damages the brain.

Seizure • June 2012

Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures

Jones NA1, Glyn SE, Akiyama S, Hill TD, Hill AJ, Weston SE, Burnett MD, Yamasaki Y, Stephens GJ, Whalley BJ, Williams CM.

School of Pharmacy, University of Reading, Whiteknights, Reading RG6 6AJ, UK
n.a.jones@reading.ac.uk

Full text, PDF, with 60 references

[http://www.seizure-journal.com/article/S1059-1311\(12\)00057-X/pdf](http://www.seizure-journal.com/article/S1059-1311(12)00057-X/pdf)

Cannabis sativa has been associated with contradictory effects upon seizure states despite its medicinal use by numerous people with epilepsy. We have recently shown that the phytocannabinoid cannabidiol (CBD) reduces seizure severity and lethality in the well-established in vivo model of pentylenetetrazole-induced generalised seizures, suggesting that earlier, small-scale clinical trials examining CBD effects in people with epilepsy warrant renewed attention. Here, we report the effects of pure CBD (1, 10 and 100mg/kg) in two other established rodent seizure models, the acute pilocarpine model of temporal lobe seizure and the penicillin model of partial seizure. Seizure activity was video recorded and scored offline using model-specific seizure severity scales. In the pilocarpine model CBD (all doses) significantly reduced the percentage of animals experiencing the most severe seizures. In the penicillin model, CBD (≥ 10 mg/kg) significantly decreased the percentage mortality as a result of seizures; CBD (all doses) also decreased the percentage of animals experiencing the most severe tonic-clonic seizures. These results extend the anti-convulsant profile of CBD; when combined with a reported absence of psychoactive effects, this evidence strongly supports CBD as a therapeutic candidate for a diverse range of human epilepsies.

Cannabinoids suppress inflammatory and neuropathic pain by targeting $\alpha 3$ glycine receptors

Xiong W1, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, Guan Y, Pan HL, Ren K, Xu Y, Zhang L.

1. Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA

Full text with 62 references

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Certain types of nonpsychoactive cannabinoids can potentiate glycine receptors (GlyRs), an important target for nociceptive regulation at the spinal level. However, little is known about the potential and mechanism of glycinergic cannabinoids for chronic pain treatment. We report that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the $\alpha 3$ GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors nor with their psychoactive side effects. NMR analysis reveals a direct interaction between CBD and S296 in the third transmembrane domain of purified $\alpha 3$ GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking the $\alpha 3$ GlyRs. Our findings suggest that the $\alpha 3$ GlyRs mediate glycinergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction.

Cannabinoids ameliorate disease progression in a model of multiple sclerosis in mice, acting preferentially through CB1 receptor-mediated anti-inflammatory effects

de Lago E1, Moreno-Martet M, Cabranes A, Ramos JA, Fernández-Ruiz J.

1. Departamento de Bioquímica y Biología Molecular, Instituto Universitario de Investigación en Neuroquímica, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain

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Multiple sclerosis (MS) is an autoimmune disease that affects the CNS and it is characterized by inflammation, demyelination, remyelination, gliosis and axonal damage that occur mainly in the spinal cord. Cannabinoids have been proposed as promising therapeutic agents in MS given their capability to alleviate specific MS symptoms (e.g., spasticity, pain). Although MS has been considered mainly an inflammatory disorder, recent evidence, however, revealed the importance of neurodegenerative events, opening the possibility that cannabinoid agonists, given their cytoprotective properties, may also serve to reduce oligodendrocyte death and axonal damage in MS. Thus, the treatment with WIN55,512-2, a potent CB(1) and CB(2) agonist, was reported to be effective to ameliorate tremor and spasticity in mice with chronic relapsing experimental autoimmune encephalomyelitis, a murine model of MS, but also to delay disease progression in this and other murine models of MS. The purpose of this investigation was to further explore the mechanism(s) underlying the amelioration in disease progression caused by WIN55,212-2. We have particularly focused on anti-glutamatergic and anti-inflammatory effects of this cannabinoid agonist. In this study, we used mice treated with myelin oligodendrocyte glycoprotein (MOG) that induces a progressive pattern of EAE and conducted the pharmacological experiments in early stages of the disease. As expected, the administration of WIN55,512-2 (5 mg/kg, i.p) had a positive effect in reducing neurological disability and improving motor coordination of EAE mice. Levels of glutamate and GABA in the spinal cord and also in the brainstem of EAE mice were similar to control animals, and, accordingly, they were not altered by the treatment with

WIN55,212-2. However, EAE mice showed some subtle alterations in mRNA levels for the glutamate transporter GLT1 and, to a lesser extent, GLAST too, changes that were altered by the treatment with WIN55,212-2 in the spinal cord, but not in the brainstem. Regarding to inflammatory responses, EAE mice showed a marked up-regulation in mRNA levels for COX-2, inducible NOS and TNF- α in the spinal cord and the brainstem, these responses being attenuated after the treatment with WIN55,212-2. We also observed the presence of cell aggregates in the spinal cord of EAE mice that were significantly attenuated by the treatment with WIN55,212-2. Immunohistochemical analysis (with Iba-1 and Cd11b) of these aggregates indicated that they corresponded to microglia (resident macrophages) and peripheral macrophages. Lastly, experiments conducted with selective antagonists for the CB(1) (e.g. rimonabant) or CB(2) (e.g. AM-630) receptors revealed that WIN55,212-2 effects in EAE mice were mediated by the activation of CB(1) but not CB(2) receptors, as reflected the reversion of positive effects of this cannabinoid on neurological decline, TNF- α generation and accumulation of cell aggregates in the spinal cord with rimonabant, but not with AM-630. This was concordant with the lack of positive effects on neurological decline observed in EAE mice when they received HU-308, a selective CB(2) receptor agonist, instead WIN55,212-2. In summary, the treatment of EAE mice with the cannabinoid agonist WIN55,512-2 reduced their neurological disability and the progression of the disease. This effect was exerted through the activation of CB(1) receptors, which would exert a positive influence in the reduction of inflammatory events linked to the pathogenesis of this disease.

Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug

Schier AR1, Ribeiro NP, Silva AC, Hallak JE, Crippa JA, Nardi AE, Zuardi AW.

1. Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro, Brazil
alexschier@hotmail.com

Full text, PDF, with 40 references

<http://www.scielo.br/pdf/rbp/v34s1/v34s1a08.pdf>

To review and describe studies of the non-psychotomimetic constituent of Cannabis sativa, cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action.

Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.

Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

Cannabidiol in Humans—The Quest for Therapeutic Targets

Simon Zornitsky¹ and Stéphane Potvin^{2,*}

¹ Multiple Sclerosis Clinic, Foothills Medical Centre, Department of Clinical Neurosciences, Faculty of Medicine, University of Calgary, Calgary, Alberta T2N 1N4, Canada

² Fernand-Seguin Research Centre, Department of Psychiatry, Faculty of Medicine, Université de Montréal, Montreal, Quebec H1N 3V2, Canada

Full text with 100 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3763649/>

Cannabidiol (CBD), a major phytocannabinoid constituent of cannabis, is attracting growing attention in medicine for its anxiolytic, antipsychotic, antiemetic and anti-inflammatory properties.

However, up to this point, a comprehensive literature review of the effects of CBD in humans is lacking. The aim of the present systematic review is to examine the randomized and crossover studies that administered CBD to healthy controls and to clinical patients. A systematic search was performed in the electronic databases PubMed and EMBASE using the key word “cannabidiol”. Both monotherapy and combination studies (e.g., CBD + Δ 9-THC) were included. A total of 34 studies were identified: 16 of these were experimental studies, conducted in healthy subjects, and 18 were conducted in clinical populations, including multiple sclerosis (six studies), schizophrenia and bipolar mania (four studies), social anxiety disorder (two studies), neuropathic and cancer pain (two studies), cancer anorexia (one study), Huntington’s disease (one study), insomnia (one study), and epilepsy (one study).

Experimental studies indicate that a high-dose of inhaled/intravenous CBD is required to inhibit the effects of a lower dose of Δ 9-THC. Moreover, some experimental and clinical studies suggest that oral/oromucosal CBD may prolong and/or intensify Δ 9-THC-induced effects, whereas others suggest that it may inhibit Δ 9-THC-induced effects. Finally, preliminary clinical trials suggest that high-dose oral CBD (150–600 mg/d) may exert a therapeutic effect for social anxiety disorder, insomnia and epilepsy, but also that it may cause mental sedation. Potential pharmacokinetic and pharmacodynamic explanations for these results are discussed.

Cannabis use and duration of untreated psychosis: a systematic review and meta-analysis

By J.K. Burns

Department of Psychiatry, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa
burns@ukzn.ac.za

<http://www.ncbi.nlm.nih.gov/pubmed/22716138>

Duration of untreated psychosis (DUP) is an important predictor of outcome in first-episode psychosis (FEP). Cannabis use is highly prevalent in FEP patients and it is important to evaluate the potential impact of cannabis use on DUP.

A systematic review of the literature was conducted to identify articles reporting DUP in FEP cannabis users (CU+) and nonusers (CU-) respectively. Studies meeting inclusion criteria were entered into a meta-analysis. In addition, a comparative review was conducted of the relationship between substance use and DUP.

Nine studies were identified reporting DUP in CU+ versus CU- patients. Of the pooled sample of 1726 FEP patients, 39% were cannabis users. Although in most studies DUP was shorter in cannabis using patients, meta-analysis did not detect a significant relationship between DUP and cannabis use. A trend towards shorter DUP in substance users was also apparent in the comparative review; although in none of the studies did this association reach statistical significance.

This review and meta-analysis suggests a trend association between shorter DUP and cannabis use in FEP; especially when cannabis use is defined in terms of current or recent use (rather than lifetime use.) Further research should aim to clarify the relative effects of longstanding versus recent onset cannabis use on neurobiology, pathway to care and outcome in FEP.

Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting

By B. Todaro

Roswell Park Cancer Institute, Buffalo, New York 14263, USA
barbara.todaro@roswellpark.org

<http://www.ncbi.nlm.nih.gov/pubmed/22491047>

Before the introduction of the serotonin receptor antagonists (5-HT₃ receptor antagonists) in the early 1990s, limited effective options were available to prevent and treat chemotherapy-induced nausea and vomiting (CINV). In 1985, the FDA approved 2 cannabinoid derivatives, dronabinol and nabilone, for the treatment of CINV not effectively treated by other agents. Today, the standard of care for prevention of CINV for highly and moderately emetogenic chemotherapy is a 5-HT₃ receptor antagonist, dexamethasone, with or without aprepitant or fosaprepitant. With the approval of safer and more effective agents, cannabinoids are not recommended as first-line treatment for the prevention of CINV and are reserved for patients with breakthrough nausea and vomiting. Because of medical and legal concerns, the use of marijuana is not recommended for management of CINV and is not part of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis. Although patients may like to pursue this treatment option in states that have approved the use of marijuana for medical purposes, its use remains legally and therapeutically controversial.

Increasing delta-9-tetrahydrocannabinol (Δ -9-THC) content in herbal cannabis over time: systematic review and meta-analysis

Cascini F1, Aiello C, Di Tanna G.

1. Istituto di Medicina Legale, Università Cattolica del S Cuore, largo F. Vito, 1 00168 Roma, Italy
f.cascini@rm.unicatt.it

<http://www.ncbi.nlm.nih.gov/pubmed/22150622>

The objective of this meta-analysis is to assess the data regarding changes in herbal cannabis potency over time (from 1970 to 2009).

Systematic searches of 17 electronic scientific databases identified studies on this topic, within which 21 case series studies satisfied our inclusion criteria of reporting the mean tetrahydrocannabinol (THC) value per number of samples per year. No language, publication date, publication type or status restrictions were imposed. The study selection and data extraction processes were performed independently but uniformly by two authors, included screening, determination of eligibility and inclusion of the eligible studies in the systematic review, and a meta-analysis of the results on THC content in herbal cannabis samples. We considered papers and not monographic scientific publications, rejecting all studies that were not focused on the subject of this review.

Meta-analysis by year was performed on 21 studies containing 75 total mean THC observations from 1979 to 2009 using the random effects model. The results revealed much variability between studies. Further, there was a significant correlation between year and mean THC in herbal cannabis. The combined data indicated the correlation between year and mean THC in herbal cannabis, revealing a temporal trend of increasing potency (5% above the mean THC value in the Poisson regression analysis).

The results of the analysis suggest that there has been a recent and consistent increase in cannabis potency worldwide.

Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

F M Leweke,^{1,2,*} D Piomelli,^{3,4,*} F Pahlisch,^{1,3} D Muhl,^{2,3} C W Gerth,² C Hoyer,^{1,2} J Klosterkötter,² M Hellmich,⁵ and D Koethe^{1,2}

1. Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

2. Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

3. Department of Pharmacology and Biological Chemistry, University of California, Irvine, CA, USA

4. The Unit of Drug Discovery and Development, Italian Institute of Technology, Genova, Italy

5. Institute for Medical Statistics, Informatics, and Epidemiology, University of Cologne, Cologne, Germany

Full text with 37 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3316151/>

Cannabidiol is a component of marijuana that does not activate cannabinoid receptors, but moderately inhibits the degradation of the endocannabinoid anandamide. We previously reported that an elevation of anandamide levels in cerebrospinal fluid inversely correlated to psychotic symptoms. Furthermore, enhanced anandamide signaling led to a lower transition rate from initial prodromal states into frank psychosis as well as postponed transition. In our translational approach, we performed a double-blind, randomized clinical trial of cannabidiol vs amisulpride, a potent antipsychotic, in acute schizophrenia to evaluate the clinical relevance of our initial findings. Either treatment was safe and led to significant clinical improvement, but cannabidiol displayed a markedly superior side-effect profile. Moreover, cannabidiol treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement. The results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia.

A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation

Zuardi AW1, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, McGuire PK, Guimarães FS.

1. Department of Neuroscience and Behavior, Faculty of Medicine, University of São Paulo and National Institute for Translational Medicine, Ribeirão Preto, SP-Brazil

<http://www.ncbi.nlm.nih.gov/pubmed/22716160>

$\Delta(9)$ -tetrahydrocannabinol ($\Delta(9)$ -THC) is the main compound of the Cannabis Sativa responsible for most of the effects of the plant. Another major constituent is cannabidiol (CBD), formerly regarded to be devoid of pharmacological activity. However, laboratory rodents and human studies have shown that this cannabinoid is able to prevent psychotic-like symptoms induced by high doses of $\Delta(9)$ -THC. Subsequent studies have demonstrated that CBD has antipsychotic effects as observed using animal models and in healthy volunteers. Thus, this article provides a critical review of the research evaluating antipsychotic potential of this cannabinoid. CBD appears to have pharmacological profile similar to that of atypical antipsychotic drugs as seen using behavioral and neurochemical techniques in animal models. Additionally, CBD prevented human experimental psychosis and was effective in open case reports and clinical trials in patients with schizophrenia with a remarkable safety profile. Moreover, fMRI results strongly suggest that the antipsychotic effects of CBD in relation to the psychotomimetic effects of $\Delta(9)$ -THC involve the striatum and temporal cortex that have been traditionally associated with psychosis. Although the mechanisms of the antipsychotic properties are still not fully understood, we propose a hypothesis that could have a heuristic value to inspire new studies. These results support the idea that CBD may be a future therapeutic option in psychosis, in general and in schizophrenia, in particular.

Cannabinoid hyperemesis [severe or prolonged vomiting]: a case series of 98 patients

Simonetto DA¹, Oxentenko AS, Herman ML, Szostek JH.

Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA

Full text with 25 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538402/>

We constructed a case series, the largest to date, of patients diagnosed with CH at our institution. Inclusion criteria were determined by reviewing all PubMed indexed journals with case reports and case series on CH. The institution's electronic medical record was searched from January 1, 2005, through June 15, 2010. Patients were included if there was a history of recurrent vomiting with no other explanation for symptoms and if cannabis use preceded symptom onset. Of 1571 patients identified, 98 patients (6%) met inclusion criteria.

All 98 patients were younger than 50 years of age. Among the 37 patients in whom duration of cannabis use was available, most (25 [68%]) reported using cannabis for more than 2 years before symptom onset, and 71 of 75 patients (95%) in whom frequency of use was available used cannabis more than once weekly. Eighty-four patients (86%) reported abdominal pain. The effect of hot water bathing was documented in 57 patients (58%), and 52 (91%) of these patients reported relief of symptoms with hot showers or baths. Follow-up was available in only 10 patients (10%). Of those 10, 7 (70%) stopped using cannabis and 6 of these 7 (86%) noted complete resolution of their symptoms.

Cannabinoid hyperemesis should be considered in younger patients with long-term cannabis use and recurrent nausea, vomiting, and abdominal pain. On the basis of our findings in this large series of patients, we propose major and supportive criteria for the diagnosis of CH.

Blurred boundaries: the therapeutics and politics of medical marijuana

By J.M. Bostwick

Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN 55905, USA
bostwick.john@mayo.edu

<http://www.ncbi.nlm.nih.gov/pubmed/22305029>

For 5 millennia, *Cannabis sativa* has been used throughout the world medically, recreationally, and spiritually. From the mid-19th century to the 1930s, American physicians prescribed it for a plethora of indications, until the federal government started imposing restrictions on its use, culminating in 1970 with the US Congress classifying it as a Schedule I substance, illegal, and without medical value. Simultaneous with this prohibition, marijuana became the United States' most widely used illicit recreational drug, a substance generally regarded as pleasurable and relaxing without the addictive dangers of opioids or stimulants. Meanwhile, cannabis never lost its cachet in alternative medicine circles, going mainstream in 1995 when California became the first of 16 states to date to legalize its medical use, despite the federal ban. Little about cannabis is straightforward. Its main active ingredient, δ -9-tetrahydrocannabinol, was not isolated until 1964, and not until the 1990s were the far-reaching modulatory activities of the endocannabinoid system in the human body appreciated. This system's elucidation raises the possibility of many promising pharmaceutical applications, even as draconian federal restrictions that hamstring research show no signs of softening. Recreational use continues unabated, despite growing evidence of marijuana's addictive potential, particularly in the young, and its propensity for inducing and exacerbating psychotic illness in the susceptible. Public approval drives medical marijuana legalization efforts without the scientific data normally required to justify a new medication's introduction. This article explores each of these controversies, with the intent of educating physicians to decide for themselves whether marijuana is panacea, scourge, or both. PubMed searches were conducted using the following keywords: medical marijuana, medical cannabis, endocannabinoid system, CB1 receptors, CB2 receptors, THC, cannabidiol, nabilone, dronabinol, nabiximols, rimonabant, marijuana legislation, marijuana abuse, marijuana dependence, and marijuana and schizophrenia. Bibliographies were hand searched for additional references relevant to clarifying the relationships between medical and recreational marijuana use and abuse.

Cannabis—a valuable drug that deserves better treatment

By R. Mechoulam

Institute for Drug Research, Medical Faculty, Hebrew University, Jerusalem, Israel

Full text with 18 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3498425/>

About 150 years ago, a French psychiatrist, J. J. Moreau, conducted a novel clinical experiment in which he administered hashish to humans. His volunteers, including Moreau himself, experienced “occurrences of delirium or of actual madness. . .” He concluded that “There is not a single, elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish. . .”¹ In contrast, most marijuana users today will presumably state that their senses appear enhanced, concomitant with an increase in relaxation and euphoria; while forgetfulness is enhanced, their focus on their surroundings is augmented.² These surprisingly contrasting experiences are due to the ingestion or smoking of products of the same plant, and neither is inaccurate if one considers the difference in doses presumably taken, the presence in cannabis (a term that includes both marijuana and hashish preparations) of at least 2 compounds with opposite effects— δ -9-tetrahydrocannabinol (THC), the psychoactive component, and cannabidiol (CBD), a nonpsychoactive constituent—and the different users’ susceptibilities to the effects of the drug. It is also well known that the activity of THC is biphasic in many assays—low and high doses may cause opposite effects.³ Presumably the Moreau volunteers consumed (orally) huge amounts of

North African hashish, which has a very high concentration of THC. However, North Americans and Europeans today generally smoke cannabis and can titrate (ie, finely adjust) the level of the psychotropic effects and thus do not typically reach the high psychotic state.

Cannabidiol modifies the effects of THC. Thus, CBD blocks anxiety provoked by THC⁴; cannabis with high CBD content is associated with fewer psychotic experiences than cannabis with low CBD content,⁵ and CBD attenuates the memory-impairing effects produced by THC.⁶ Cannabidiol is also a potent anti-inflammatory compound and has an anti-autoimmune diabetes effect (in a mouse model).⁷ However, most users are not aware of the amounts of THC and CBD in the cannabis they use. Most of the marijuana sold illegally today in the United States actually contains no CBD, or very low amounts of it, and the THC levels in marijuana may vary from about 3% to 25%. These large variations of THC levels are due mainly to the different sources of the drug, but even samples from the same source may vary, depending on the portion of the plant and the plant’s age. Hence, much of the statistics based on “street users” is quite useless.

Modern medical practice is based on the administration of defined levels of drugs. Most physicians are not comfortable prescribing a plant product with varying concentrations of active pharmacological compounds, and certainly no other prescribed drug is administered by smoking. However, from a medical point of view, marijuana is a valuable drug. It lowers certain types of pain; has antianxiety, anti-inflammatory, and antispastic effects; and enhances appetite.³ Its adverse effects are also well known. It can precipitate anxiety attacks or even schizophrenia in susceptible individuals, although, surprisingly, the extent of schizophrenia in the general population does not seem to have increased in parallel with the very wide use of marijuana for recreational purposes. The United Nations Office on Drugs and Crime has estimated that in 2006 cannabis was used (presumably mostly for recreation) by 166 million adults.⁸ Dependence to cannabis has been noted in about 9% of heavy users.⁸

Recent research has shown that many of the therapeutic effects of cannabinoids are not due solely to the cannabinoid CB1 receptors, whose stimulation causes the cannabis psychoactivity, but also to CB2 receptor activation, which causes no psychoactivity but attenuates inflammation, decreases injury, and accelerates regeneration in many disease states.⁹ However, essentially all the published research on specific CB2 stimulation has been done in animals.

The current issue of Mayo Clinic Proceedings has 2 articles on cannabis. One of them, by Simonetto et al, deals with the rather uncommon severe vomiting seen in some “street marijuana” users.¹⁰ The other, by Bostwick, is a general review on the therapeutic effects of cannabis and the politics of medical use of marijuana.¹¹

Hyperemesis is not an acute effect of cannabis smoking. In the case series reported by Simonetto et al,¹⁰ hyperemesis appeared in most patients after more than 2 years of smoking at least once a week. Surprisingly, most patients (83%) had lost weight (median loss, 12 kg), and 23% had diarrhea. These are not effects expected in cannabis users. On the contrary, THC is known to block vomiting,¹² enhance appetite,¹³ and cause constipation.¹⁴ The authors do not discuss these observations, but it is tempting to speculate that an endogenous CB1 receptor antagonist-like compound is produced as a result of prolonged THC use, perhaps involving some form of a novel “cannabinoid immune-type reaction.” If this speculation is correct, such an endogenous CB1 receptor antagonist would be expected to block some physiologic processes affected by THC. Indeed, synthetic CB1 receptor blockers are known to cause weight loss,^{15,16} induce nausea,¹⁵ and increase defecation.¹⁷ Other mechanisms of the hyperemesis are also conceivable. Simonetto et al suggest that “the central effects of long-term cannabis use on the hypothalam-

ic-pituitary-adrenal axis might play a major role in the development of [cannabinoid hyperemesis].” While these suggestions have a certain intellectual appeal, we should not forget that the quality of the material used by these patients is unknown and that we know nothing about the presence (or levels) of additional cannabis constituents or foreign substances (most commonly pesticides) with unknown pharmacological effects that may have been included in the street marijuana consumed. Hence, although the direct connection between hyperemesis and cannabis seems reasonable, full proof is lacking. Nevertheless, the authors’ viewpoint is of clinical importance: “Given the prevalence of cannabis use worldwide, the very recent recognition of [cannabinoid hyperemesis], and the paucity of [cannabinoid hyperemesis] literature, it is likely that this disease is underrecognized and underdiagnosed.”

The article by Bostwick deals with the therapeutics and politics of medical use of marijuana. He has critically and very well presented both aspects. In most countries, including the United States, marijuana is a Schedule I controlled substance (high potential for abuse; no currently accepted medical use). Like individuals, countries can also be hypocritical. In contrast to marijuana, THC, also called dronabinol, is a Schedule III drug (has potential for abuse less than that of substances in Schedules I or II). Dronabinol is an approved drug in the United States and numerous other countries for several medical conditions, mostly as an antiemetic during cancer chemotherapy and to improve appetite in patients with human immunodeficiency virus. Nabilone, marketed as Cesamet, a synthetic analogue of THC, is actually a Schedule II drug (high potential for abuse) and is prescribed for similar indications. It parallels the effects of THC, although it is more potent and its activity persists longer than that of THC. A 50:50 THC:CBD mixture of cannabis plant origin (named Sativex) is in medical use as an oral spray in many European countries,

as well as in Canada. There is also a plethora of articles on the therapeutic effects of marijuana. For example, Abrams et al¹⁸ recently showed that “vaporized cannabis augments analgesia in individuals with chronic pain on a treatment regimen of stable doses of sustained-release morphine or oxycodone, and that the mechanism of augmentation is not explained by elevation of plasma opioid concentrations or inhibition of opioid metabolism.” Aren’t all the aforementioned evidence of “currently accepted medical use”?

In his article, Bostwick points out that “[a]s the mysteries of the endocannabinoid system were unraveled . . . , a rationale for both its recreational and sweeping medical effects has emerged,” and he therefore recommends that marijuana should be rescheduled as something other than Schedule I. This rescheduling, Bostwick argues, would facilitate future research on marijuana. Whether intended by him or not, it also would make marijuana available by prescription. The presence of 2 active compounds in cannabis may open the possibility of individualized treatment. By modifying the ratio of THC:CBD, it should be possible to establish a personal dose for specific patients, depending on the diagnosis and the individual susceptibility. However, to make such treatment possible, we should demand that medical marijuana be supplied with an analysis of at least its 2 major constituents and that a variety of mixtures should be available. Various types of marijuana preparations for oral administration should also be attainable.

Research on specific CB2 receptor agonists promises to lead to novel drugs, which may, in part at least, diminish the need for medical marijuana. Nevertheless, I believe that medical marijuana as a therapeutic entity is here to stay. It is being used in numerous medical conditions, at times with considerable success. Are we entitled to neglect a valuable drug?

Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being

Morgan CJ1, Gardener C1, Schafer G1, Swan S1, Demarchi C1, Freeman TP1, Warrington P1, Rupasinghe I1, Ramoutar A1, Tan N1, Wingham G1, Lewis S1, Curran HV1.

<http://www.ncbi.nlm.nih.gov/pubmed/21798112>

Cannabis varies considerably in levels of its two major constituent cannabinoids - (delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Recently, we found evidence that those who smoked cannabis containing detectable levels of CBD had fewer psychotic-like symptoms than those whose cannabis had no CBD. The present study aimed, first, to replicate those findings and, second, to determine whether protective effects of CBD may extend to other harms of cannabis, such as memory impairment and reduced psychological well-being.

A total of 120 current cannabis smokers, 66 daily users and 54 recreational users were classified into groups according to whether analysis of their hair revealed the presence or absence of CBD and high versus low levels of THC. All were assessed on measures of psychosis-like symptoms, memory (prose recall; source memory) and depression/anxiety.

Lower psychosis-like symptoms were found in those whose hair had CBD compared with those without. However, this was seen only in recreational users, who had higher levels of THC in their hair. Higher THC levels in hair were associated with increased depression and anxiety. Prose recall and source memory were poorer in daily users with high THC levels in hair while recognition memory was better in individuals with CBD present in hair.

CBD attenuates the psychotic-like effects of cannabis over time in recreational users. Higher THC negatively impacts on memory and psychological well-being. These findings raise concerns for the harms stemming from use of varieties such as 'skunk' (sensimillia), which lack any CBD but currently dominate the supply of cannabis in many countries.

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Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls

Cousijn J1, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE.

ADAPT-lab, Department of Psychology, University of Amsterdam, The Netherlands
j.cousijn@uva.nl

<http://www.ncbi.nlm.nih.gov/pubmed/21982932>

Cannabis abuse is related to impairments in a broad range of cognitive functions. However, studies on cannabis abuse in relation to brain structure are sparse and results are inconsistent, probably due to differences in imaging methodology, severity of cannabis abuse, and use of other substances. The goal of the current MRI study was to investigate brain morphology related to current and lifetime severity of cannabis use and dependence in heavy cannabis users without intensive use of other illicit drugs. Voxel-based morphometry was used to assess differences in regional grey and white matter volume between 33 heavy cannabis users and 42 matched controls. Within heavy cannabis users, grey and white matter volume was correlated with measures of cannabis use and dependence. Analyses were focused a priori on the orbitofrontal cortex, anterior cingulate cortex, striatum, amygdala, hippocampus, and cerebellum, regions implicated in substance dependence and/or with high cannabinoid receptor-1 concentrations. Regional grey matter volume in the anterior cerebellum was larger in heavy cannabis users. Within the group of heavy cannabis users, grey matter volume in the amygdala and hippocampus correlated negatively with the amount of cannabis use or dependence. No associations were found between white matter volume and measures of cannabis use or dependence. These findings indicate that associations between heavy cannabis use and altered brain structure are complex. Differential patterns of structural changes for various cannabis use levels imply that alterations in brain structure are associated with specific characteristics of cannabis use and dependence.

Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarin (CBDV), Δ^9 -tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour

Deiana S1, Watanabe A, Yamasaki Y, Amada N, Arthur M, Fleming S, Woodcock H, Dorward P, Pigliacampo B, Close S, Platt B, Riedel G.

<http://www.ncbi.nlm.nih.gov/pubmed/21796370>

Phytocannabinoids are useful therapeutics for multiple applications including treatments of constipation, malaria, rheumatism, alleviation of intraocular pressure, emesis, anxiety and some neurological and neurodegenerative disorders. Consistent with these medicinal properties, extracted cannabinoids have recently gained much interest in research, and some are currently in advanced stages of clinical testing. Other constituents of *Cannabis sativa*, the hemp plant, however, remain relatively unexplored in vivo. These include cannabidiol (CBD), cannabidivarin (CBDV), $\Delta(9)$ -tetrahydrocannabivarin ($\Delta(9)$ -THCV) and cannabigerol (CBG).

All phytocannabinoids readily penetrated the blood-brain barrier and solutol, despite producing moderate behavioural anomalies, led to higher brain penetration than cremophor after oral, but not intraperitoneal exposure. In mice, cremophor-based intraperitoneal administration always attained higher plasma and brain concentrations, independent of substance given. In rats, oral administration offered higher brain concentrations for CBD (120 mg/kg) and CBDV (60 mg/kg), but not for $\Delta(9)$ -THCV (30 mg/kg) and CBG (120 mg/kg), for which the intraperitoneal route was more effective. CBD inhibited obsessive-compulsive behaviour in a time-dependent manner matching its pharmacokinetic profile.

These data provide important information on the brain and plasma exposure of new phytocannabinoids and guidance for the most efficacious administration route and time points for determination of drug effects under in vivo conditions.

Searching for health beneficial n-3 and n-6 fatty acids in plant seeds

Kuhnt K1, Degen C, Jaudszus A, Jahreis G.

Institute of Nutrition, Department of Nutritional Physiology, Friedrich Schiller University Jena, Germany

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380567/>

Various plant seeds have received little attention in fatty acid research. Seeds from 30 species mainly of Boraginaceae and Primulaceae were analysed in order to identify potential new sources of the n-3 PUFA α -linolenic acid (ALA) and stearidonic acid (SDA) and of the n-6 PUFA γ -linolenic acid (GLA).

Cannabis sativa cultivars (Cannabaceae) were rich in linoleic acid (57.1%), but poor in SDA and GLA (0.8, 2.7%, resp.). In conclusion, several of the presented plant seeds contain considerable amounts of n-3 PUFA and GLA, which could be relevant for nutritional purposes due to their biological function as precursors for eicosanoid synthesis.

N-3 PUFA are important for human health and nutrition. Unfortunately, due to the increasing world population, over-fishing of the seas and generally low amounts of n-3 PUFA in major oil crops, there is a demand for new sources of n-3 PUFA. One approach involves searching for potential vegetable sources of n-3 PUFA; especially those rich in ALA and SDA. The conversion of ALA to SDA in humans is dependent on the rate-limiting $\Delta 6$ -desaturation. Plant-derived SDA is therefore a promising precursor regarding the endogenous synthesis of n-3 long-chain PUFA in humans.

The present study shows that, in addition to seed oil of *Echium*, other species of Boraginaceae (*Cerithe*, *Omphalodes*, *Lithospermum*, *Buglossoides*) and Primulaceae (*Dodecatheon*, *Primula*), generally high in n-3 PUFA (30-50%), contain considerable amounts of SDA (5-10%). Therefore, these seed oils could be important for nutrition.

Neurotoxicology & Teratology • January 2012

School achievement in 14-year-old youths prenatally exposed to marijuana

Goldschmidt L1, Richardson GA, Willford JA, Severtson SG, Day NL.

Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA
lidush@pitt.edu

Full text with 51 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3260381/>

The relation between prenatal marijuana exposure (PME) and school achievement was evaluated in a sample of 524 14-year-olds. Women were recruited during pregnancy and assessed, along with their offspring, at multiple phases from infancy to early adulthood. The sample represents a low-income population. Half of the adolescents are male and 55% are African American. School achievement was assessed with the Wechsler Individual Achievement Test (WIAT) Screener (Psychological Corporation, 1992). A significant negative relation was found between PME and 14-year WIAT composite and reading scores. The deficit in school achievement was mediated by the effects of PME on intelligence test performance at age 6, attention problems and depression symptoms at age 10, and early initiation of marijuana use. These findings suggest that the effects of PME on adolescent achievement are mediated by the earlier negative effects of PME on child characteristics. The negative impact of these characteristics on adolescent achievement may presage later problems in early adulthood.

Phytocannabinoids as novel therapeutic agents in CNS disorders

Hill AJ1, Williams CM, Whalley BJ, Stephens GJ.

1. School of Pharmacy, University of Reading, Whiteknights, Reading, RG6 6UB, UK

<http://www.ncbi.nlm.nih.gov/pubmed/21924288>

The *Cannabis sativa* herb contains over 100 phytocannabinoid (pCB) compounds and has been used for thousands of years for both recreational and medicinal purposes.

In the past two decades, characterisation of the body's endogenous cannabinoid (CB) (endocannabinoid, eCB) system (ECS) has highlighted activation of central CB(1) receptors by the major pCB, $\Delta(9)$ -tetrahydrocannabinol ($\Delta(9)$ -THC) as the primary mediator of the psychoactive, hyperphagic and some of the potentially therapeutic properties of ingested cannabis. Whilst $\Delta(9)$ -THC is the most prevalent and widely studied pCB, it is also the predominant psychotropic component of cannabis, a property that likely limits its widespread therapeutic use as an isolated agent. In this regard, research focus has recently widened to include other pCBs including cannabidiol (CBD), cannabigerol (CBG), $\Delta(9)$ tetrahydrocannabivarin ($\Delta(9)$ -THCV) and cannabidivarin (CBDV), some of which show potential as therapeutic agents in preclinical models of CNS disease. Moreover, it is becoming evident that these non- $\Delta(9)$ -THC pCBs act at a wide range of pharmacological targets, not solely limited to CB receptors. Disorders that could be targeted include epilepsy, neurodegenerative diseases, affective disorders and the central modulation of feeding behaviour. Here, we review pCB effects in preclinical models of CNS disease and, where available, clinical trial data that support therapeutic effects. Such developments may soon yield the first non- $\Delta(9)$ -THC pCB-based medicines.

A high-angle, close-up photograph of a dense field of cannabis plants. The plants are in various stages of growth, with many showing prominent, serrated, palmate leaves. The color is a vibrant green, with some leaves showing slight yellowing or damage. The background is a dark, rich brown soil, which makes the green foliage stand out. The overall texture is very busy and organic.

CANNABIS • 1964 - 2011 PEER REVIEW

Medical Science Monitor • December 2011

Medical marijuana: medical necessity versus political agenda

Clark PA1, Capuzzi K, Fick C.

Jesuit Community, St Joseph's University, Philadelphia, PA 19131, USA
pclark@sju.edu

Full text with 89 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628147/>

Marijuana is classified by the Drug Enforcement Agency (DEA) as an illegal Schedule I drug which has no accepted medical use. However, recent studies have shown that medical marijuana is effective in controlling chronic non-cancer pain, alleviating nausea and vomiting associated with chemotherapy, treating wasting syndrome associated with AIDS, and controlling muscle spasms due to multiple sclerosis. These studies state that the alleviating benefits of marijuana outweigh the negative effects of the drug, and recommend that marijuana be administered to patients who have failed to respond to other therapies. Despite supporting evidence, the DEA refuses to reclassify marijuana as a Schedule II drug, which would allow physicians to prescribe marijuana to suffering patients. The use of medical marijuana has continued to gain support among states, and is currently legal in 16 states and the District of Columbia. This is in stark contrast to the federal government's stance of zero-tolerance, which has led to a heated legal debate in the United States. After reviewing relevant scientific data and grounding the issue in ethical principles like beneficence and nonmaleficence, there is a strong argument for allowing physicians to prescribe marijuana. Patients have a right to all beneficial treatments and to deny them this right violates their basic human rights.

The multiplicity of action of cannabinoids: implications for treating neurodegeneration

Gowran A1, Noonan J, Campbell VA.

1. Department of Physiology, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

<http://www.ncbi.nlm.nih.gov/pubmed/20875047>

The cannabinoid (CB) system is widespread in the central nervous system and is crucial for controlling a range of neurophysiological processes such as pain, appetite, and cognition. The endogenous CB molecules, anandamide, and 2-arachidonoyl glycerol, interact with the G-protein coupled CB receptors, CB(1) and CB(2). These receptors are also targets for the phytocannabinoids isolated from the cannabis plant and synthetic CB receptor ligands. The CB system is emerging as a key regulator of neuronal cell fate and is capable of conferring neuroprotection by the direct engagement of prosurvival pathways and the control of neurogenesis. Many neurological conditions feature a neurodegenerative component that is associated with excitotoxicity, oxidative stress, and neuroinflammation, and certain CB molecules have been demonstrated to inhibit these events to halt the progression of neurodegeneration. Such properties are attractive in the development of new strategies to treat neurodegenerative conditions of diverse etiology, such as Alzheimer's disease, multiple sclerosis, and cerebral ischemia. This article will discuss the experimental and clinical evidence supporting a potential role for CB-based therapies in the treatment of certain neurological diseases that feature a neurodegenerative component.

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Lynch ME1, Campbell F.

Department Anesthesia, Psychiatry, Dalhousie University, Halifax, Canada
mary.lynch@dal.ca

Full text with 52 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243008/>

Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to the PRISMA statement update on the QUORUM guidelines for reporting systematic reviews that evaluate health care interventions. Cannabinoids studied included smoked cannabis, oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a novel THC analogue. Chronic non-cancer pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Overall the quality of trials was excellent. Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. The context of the need for additional treatments for chronic pain is reviewed. Further large studies of longer duration examining specific cannabinoids in homogeneous populations are required.

Digestion • November 2011

Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study

Lahat A1, Lang A, Ben-Horin S.

1. Department of Gastroenterology, Chaim Sheba Medical Center affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
zokadi@gmail.com

<http://www.ncbi.nlm.nih.gov/pubmed/22095142>

Inflammatory bowel disease (IBD) patients suffer from significant morbidity and diminished life quality. The plant cannabis is beneficial in various gastrointestinal diseases, stimulating appetite and causing weight gain. Our aims were to assess whether treatment with inhaled cannabis improves quality of life, disease activity and promotes weight gain in these patients.

Three months' treatment with inhaled cannabis improves quality of life measurements, disease activity index, and causes weight gain and rise in BMI in long-standing IBD patients.

Cannabis use amongst patients with inflammatory bowel disease

Lal S1, Prasad N, Ryan M, Tangri S, Silverberg MS, Gordon A, Steinhart H.

1. The IBD Clinic, Mount Sinai Hospital, Toronto, Ontario, Canada
simon.lal@srft.nhs.uk

<http://www.ncbi.nlm.nih.gov/pubmed/21795981>

Experimental evidence suggests the endogenous cannabinoid system may protect against colonic inflammation, leading to the possibility that activation of this system may have a therapeutic role in inflammatory bowel disease (IBD). Medicinal use of cannabis for chronic pain and other symptoms has been reported in a number of medical conditions. We aimed to evaluate cannabis use in patients with IBD.

One hundred patients with ulcerative colitis (UC) and 191 patients with Crohn's disease (CD) attending a tertiary-care outpatient clinic completed a questionnaire regarding current and previous cannabis use, socioeconomic factors, disease history and medication use, including complimentary alternative medicines. Quality of life was assessed using the short-inflammatory bowel disease questionnaire.

Cannabis use is common amongst patients with IBD for symptom relief, particularly amongst those with a history of abdominal surgery, chronic abdominal pain and/or a low quality of life index. The therapeutic benefits of cannabinoid derivatives in IBD may warrant further exploration.

Safety and side effects of cannabidiol, a Cannabis sativa constituent

Bergamaschi MM1, Queiroz RH, Zuardi AW, Crippa JA.

1. Department of Clinical, Toxicological and Food Sciences Analysis, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, SP, Brazil

<http://www.ncbi.nlm.nih.gov/pubmed/22129319>

Cannabidiol (CBD), a major nonpsychotropic constituent of Cannabis, has multiple pharmacological actions, including anxiolytic, antipsychotic, antiemetic and anti-inflammatory properties. However, little is known about its safety and side effect profile in animals and humans. This review describes *in vivo* and *in vitro* reports of CBD administration across a wide range of concentrations, based on reports retrieved from Web of Science, Scielo and Medline. The keywords searched were “cannabinoids”, “cannabidiol” and “side effects”. Several studies suggest that CBD is non-toxic in non-transformed cells and does not induce changes on food intake, does not induce catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature), does not affect gastrointestinal transit and does not alter psychomotor or psychological functions. Also, chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans. Conversely, some studies reported that this cannabinoid can induce some side effects, including inhibition of hepatic drug metabolism, alterations of *in vitro* cell viability, decreased fertilization capacity, and decreased activities of p-glycoprotein and other drug transporters. Based on recent advances in cannabinoid administration in humans, controlled CBD may be safe in humans and animals. However, further studies are needed to clarify these reported *in vitro* and *in vivo* side effects.

The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease

Di Sabatino A1, Battista N, Biancheri P, Rapino C, Rovedatti L, Astarita G, Vanoli A, Dainese E, Guerri M, Piomelli D, Pender SL, MacDonald TT, Maccarrone M, Corazza GR.

1. First Department of Medicine, Fondazione IRCCS Policlinico S. Matteo, Centro per lo Studio e la Cura delle Malattie Infiammatorie Croniche Intestinali, University of Pavia, Pavia, Italy
a.disabatino@smatteo.pv.it

<http://www.ncbi.nlm.nih.gov/pubmed/21471961>

Activation of cannabinoid receptors (CBs) by endocannabinoids impacts on a number of gastrointestinal functions. Recent data indicate that CB1 agonists improve 2,4-dinitrobenzene sulfonic acid-induced colitis in mice, thus suggesting a role for the endocannabinoid agonist anandamide (AEA) in protecting the gut against inflammation. We here examined the gut endocannabinoid system in inflammatory bowel disease (IBD) patients, and investigated the ex vivo and in vitro effects of the non-hydrolysable AEA analog methanandamide (MAEA) on the mucosal pro-inflammatory response. The content of AEA, but not of 2-arachidonoyl-glycerol and N-palmitoylethanolamine, was significantly lower in inflamed than uninflamed IBD mucosa, and this was paralleled by lower activity of the AEA-synthesizing enzyme N-acyl-phosphatidylethanolamine-specific phospholipase D and higher activity of the AEA-degrading enzyme fatty acid amide hydrolase. MAEA significantly downregulated interferon- γ and tumor necrosis factor- α secretion by both organ culture biopsies and lamina propria mononuclear cells. Although these results are promising, further studies are needed to determine the role of cannabinoid pathways in gut inflammation.

Cannabis with high cannabidiol content is associated with fewer psychotic experiences

Schubart CD1, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP.

Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Department of Psychiatry, The Netherlands
c.schubart@umcutrecht.nl

<http://www.ncbi.nlm.nih.gov/pubmed/21592732>

Cannabis is associated with psychotic outcomes in numerous studies, an effect that is commonly attributed to Δ (9)-tetrahydrocannabinol (Δ 9-THC). An increasing number of authors identify cannabidiol, another component of the cannabis plant, as an antipsychotic agent. The objective of the current study is to investigate the role of cannabidiol content in the association between cannabis use and psychiatric symptoms in a large non-clinical population of cannabis users.

In a web-based cross-sectional study we obtained detailed information about cannabis use and subclinical psychiatric experiences using the Community Assessment of Psychic Experiences (CAPE). Different types of cannabis (i.e. marijuana, hashish etc.) have distinctive proportions of Δ 9-THC and cannabidiol. Since average concentrations of Δ 9-THC and cannabidiol in the most popular types of cannabis sold on the Dutch market are annually measured, we were able to estimate exposure to Δ 9-THC and cannabidiol.

We included 1877 subjects (mean age 23, SD 6.0) who used the same type of cannabis in the majority of the occasions (in >60% of occasions). We found a significant inverse relationship ($F(1,1877): 14.577, p<0.001$) between cannabidiol content and self-reported positive symptoms, but not with negative symptoms or depression. The estimated effect size of cannabidiol content was small.

Although the observed effects are subtle, using high cannabidiol content cannabis was associated with significantly lower degrees of psychotic symptoms providing further support for the antipsychotic potential of cannabidiol.

The atypical cannabinoid O-1602 protects against experimental colitis and inhibits neutrophil recruitment

Schicho R1, Bashashati M, Bawa M, McHugh D, Saur D, Hu HM, Zimmer A, Lutz B, Mackie K, Bradshaw HB, McCafferty DM, Sharkey KA, Storr M.

Full text with 56 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3116968/>

Cannabinoids are known to reduce intestinal inflammation. Atypical cannabinoids produce pharmacological effects via unidentified targets. We were interested in whether the atypical cannabinoid O-1602, reportedly an agonist of the putative cannabinoid receptor GPR55, reduces disease severity of dextran sulfate sodium (DSS) and trinitrobenzene sulfonic acid (TNBS)-induced colitis in C57BL/6N and CD1 mice.

DSS (2.5% and 4%) was supplied in drinking water for 1 week while TNBS (4 mg) was applied as a single intrarectal bolus. Both treatments caused severe colitis. Injection of O-1602 (5 mg/kg intraperitoneally) significantly reduced macroscopic and histological colitis scores, and myeloperoxidase activity. The protective effect was still present in cannabinoid receptor 1 (CB₁) and 2 (CB₂) double knockout mice and mice lacking the GPR55 gene. To investigate a potential mechanism underlying the protection by O-1602 we performed neutrophil chemotactic assays. O-1602 concentration-dependently inhibited migration of murine neutrophils to keratinocyte-derived chemokine (KC), N-formyl-methionyl-leucyl-phenylalanine (fMLP), and the N-formyl-peptide receptor ligand WKYMVm. The inhibitory effect of O-1602 was preserved in neutrophils from CB₁/CB₂ double knockout and GPR55 knockout mice. No differences were seen in locomotor activity between O-1602-treated and control mice, indicating lack of central sedation by this compound.

Our data demonstrate that O-1602 is protective against experimentally induced colitis and inhibits neutrophil recruitment independently of CB₁, CB₂, and GPR55 receptors. Thus, atypical cannabinoids represent a novel class of therapeutics that may be useful for the treatment of inflammatory bowel diseases.

Medial temporal structures and memory functions in adolescents with heavy cannabis use

Ashtari M1, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, Gee J, Sevy S, Kumra S.

1. Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA 19102, USA

Full text with 137 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3303223/>

Converging lines of evidence suggest an adverse effect of heavy cannabis use on adolescent brain development, particularly on the hippocampus. In this preliminary study, we compared hippocampal morphology in 14 "treatment-seeking" adolescents (aged 18-20) with a history of prior heavy cannabis use (5.8 joints/day) after an average of 6.7 months of drug abstinence, and 14 demographically matched normal controls. Participants underwent a high-resolution 3D MRI as well as cognitive testing including the California Verbal Learning Test (CVLT). Heavy-cannabis users showed significantly smaller volumes of the right ($p < 0.04$) and left ($p < 0.02$) hippocampus, but no significant differences in the amygdala region compared to controls. In controls, larger hippocampus volumes were observed to be significantly correlated with higher CVLT verbal learning and memory scores, but these relationships were not observed in cannabis users. In cannabis users, a smaller right hippocampus volume was correlated with a higher amount of cannabis use ($r = -0.57, p < 0.03$). These data support a hypothesis that heavy cannabis use may have an adverse effect on hippocampus development. These findings, after an average 6.7 month of supervised abstinence, lend support to a theory that cannabis use may impart long-term structural and functional damage. Alternatively, the observed hippocampal volumetric abnormalities may represent a risk factor for cannabis dependence. These data have potential significance for understanding the observed relationship between early cannabis exposure during adolescence and subsequent development of adult psychopathology reported in the literature for schizophrenia and related psychotic disorders.

Prospects for cannabinoid therapies in basal ganglia disorders

Fernández-Ruiz J1, Moreno-Martet M, Rodríguez-Cueto C, Palomo-Garo C, Gómez-Cañas M, Valdeolivas S, Guaza C, Romero J, Guzmán M, Mechoulam R, Ramos JA.

1. Departamento de Bioquímica y Biología Molecular III, Instituto Universitario de Investigación en Neuroquímica, Facultad de Medicina, Universidad Complutense, Madrid, Spain
jjfr@med.ucm.es

Full text with 114 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165947/>

Cannabinoids are promising medicines to slow down disease progression in neurodegenerative disorders including Parkinson's disease (PD) and Huntington's disease (HD), two of the most important disorders affecting the basal ganglia. Two pharmacological profiles have been proposed for cannabinoids being effective in these disorders. On the one hand, cannabinoids like $\Delta(9)$ -tetrahydrocannabinol or cannabidiol protect nigral or striatal neurons in experimental models of both disorders, in which oxidative injury is a prominent cytotoxic mechanism. This effect could be exerted, at least in part, through mechanisms independent of CB(1) and CB(2) receptors and involving the control of endogenous antioxidant defences. On the other hand, the activation of CB(2) receptors leads to a slower progression of neurodegeneration in both disorders. This effect would be exerted by limiting the toxicity of microglial cells for neurons and, in particular, by reducing the generation of proinflammatory factors. It is important to mention that CB(2) receptors have been identified in the healthy brain, mainly in glial elements and, to a lesser extent, in certain subpopulations of neurons, and that they are dramatically up-regulated in response to damaging stimuli, which supports the idea that the cannabinoid system behaves as an endogenous neuroprotective system. This CB(2) receptor up-regulation has been found in many neurodegenerative disorders including HD and PD, which supports the beneficial effects found for CB(2) receptor agonists in both disorders. In conclusion, the evidence reported so far supports that those cannabinoids having antioxidant properties and/or capability to activate CB(2) receptors may represent promising therapeutic agents in HD and PD, thus deserving a prompt clinical evaluation.

Effects of smoking cannabis on lung function

Lee MH1, Hancox RJ.

Department of Respiratory Medicine, Waikato Hospital, Pembroke St, Hamilton, New Zealand

<http://www.ncbi.nlm.nih.gov/pubmed/21859273>

Although cannabis (or marijuana) is the world's most widely-used illicit drug, there has been surprisingly little research into its effects on respiratory health. Part of the problem is the inherent difficulty of studying the long-term effects of an illegal habit. It has often been assumed that smoking cannabis will have similar long-term effects to smoking tobacco. Several recent observational studies suggest that this is not the case and that cannabis has quite different effects on the lung function.

There are consistent findings that smoking cannabis is associated with large airway inflammation, symptoms of bronchitis, increased airway resistance and lung hyperinflation. The evidence that smoking cannabis leads to features of chronic obstructive pulmonary disease, such as air-flow obstruction and emphysema is not convincing. However, there are numerous case reports of bullous emphysema among cannabis smokers. These findings have not been confirmed in systematic analytical studies and probably represent uncommon adverse effects in very heavy cannabis smokers. There is now additional controversial evidence that cannabis is at least an occasional cause of respiratory malignancies, but again the evidence is inconclusive.

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

By E.B. Russo

GW Pharmaceuticals, Salisbury, Wiltshire, UK
ethanrusso@comcast.net

Full text with 225 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/>

Tetrahydrocannabinol (THC) has been the primary focus of cannabis research since 1964, when Raphael Mechoulam isolated and synthesized it.

More recently, the synergistic contributions of cannabidiol to cannabis pharmacology and analgesia have been scientifically demonstrated. Other phytocannabinoids, including tetrahydrocannabivarin, cannabigerol and cannabichromene, exert additional effects of therapeutic interest. Innovative conventional plant breeding has yielded cannabis chemotypes expressing high titres of each component for future study. This review will explore another echelon of phytotherapeutic agents, the cannabis terpenoids: limonene, myrcene, α -pinene, linalool, β -caryophyllene, caryophyllene oxide, nerolidol and phytol. Terpenoids share a precursor with phytocannabinoids, and are all flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air at serum levels in the single digits $\text{ng}\cdot\text{mL}^{-1}$. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Particular focus will be placed on phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant *Staphylococcus aureus*). Scientific evidence is presented for non-cannabinoid plant components as putative antidotes to intoxicating effects of THC that could increase its therapeutic index. Methods for investigating entourage effects in future experiments will be proposed.

Phytocannabinoid-terpenoid synergy, if proven, increases the likelihood that an extensive pipeline of new therapeutic products is possible from this venerable plant.

Drug And Alcohol Dependency • August 2011

Heterogeneity in the composition of marijuana seized in California

Burgdorf JR1, Kilmer B, Pacula RL.

Pardee RAND Graduate School, RAND Corporation, 1776 Main Street, Santa Monica, CA 90401, USA

Full text with 22 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3118261/>

Marijuana contains multiple cannabinoids. Most attention is given to delta-9-tetrahydrocannabinol (THC) which produces euphoria and in some cases anxiety and panic reactions. Research suggests that another cannabinoid, cannabidiol (CBD), may offset some of these effects. Thus, there is growing interest in the health consequences of the THC to CBD ratio for marijuana.

Using data from over 5000 marijuana samples in California from 1996 to 2008, we examine changes in the median THC-level, median CBD-level, and median THC:CBD-ratio.

The median THC-level and median THC:CBD-ratio have dramatically increased for seizures in California, particularly north of the Mexican border.

Research on the consequences of the THC:CBD ratio should continue, especially as more attention is devoted to thinking about how to regulate marijuana for medical and recreational use. Researchers should also consider the lack of uniformity in the chemical composition of marijuana when evaluating its health effects.

Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes

De Petrocellis L1, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, Stott CG, Di Marzo V.

1. Endocannabinoid Research Group, Institute of Cybernetics, CNR, Pozzuoli (NA), Italy

Full text with 75 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165957/>

Cannabidiol (CBD) and $\Delta(9)$ -tetrahydrocannabinol (THC) interact with transient receptor potential (TRP) channels and enzymes of the endocannabinoid system.

The effects of 11 pure cannabinoids and botanical extracts [botanical drug substance (BDS)] from Cannabis varieties selected to contain a more abundant cannabinoid, on TRPV1, TRPV2, TRPM8, TRPA1, human recombinant diacylglycerol lipase α (DAGL α), rat brain fatty acid amide hydrolase (FAAH), COS cell monoacylglycerol lipase (MAGL), human recombinant N-acyl-ethanolamine acid amide hydrolase (NAAA) and anandamide cellular uptake (ACU) by RBL-2H3 cells, were studied using fluorescence-based calcium assays in transfected cells and radiolabelled substrate-based enzymatic assays. Cannabinol (CBN), cannabichromene (CBC), the acids (CBDA, CBGA, THCA) and propyl homologues (CBDV, CBGV, THCV) of CBD, cannabigerol (CBG) and THC, and tetrahydrocannabivarin acid (THCVA) were also tested.

These results are relevant to the analgesic, anti-inflammatory and anti-cancer effects of cannabinoids and Cannabis extracts.

Altered prefrontal and insular cortical thickness in adolescent marijuana users

Lopez-Larson MP1, Bogorodzki P, Rogowska J, McGlade E, King JB, Terry J, Yurgelun-Todd D.

The Brain Institute, University of Utah, Salt Lake City, UT 84108, USA
mlopez-larson@hsc.utah.edu

Full text with 97 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3073407/>

There are limited data regarding the impact of marijuana (MJ) on cortical development during adolescence. Adolescence is a period of substantial brain maturation and cortical thickness abnormalities may be indicative of disruptions of normal cortical development. This investigation applied cortical-surface based techniques to compare cortical thickness measures in MJ using adolescents compared to non-using controls.

This is one of the first studies to evaluate cortical thickness in a group of adolescents with heavy MJ use compared to non-users. Our findings are consistent with prior studies that documented abnormalities in prefrontal and insular regions.

Our results suggest that age of regular use may be associated with altered prefrontal cortical gray matter development in adolescents. Furthermore, reduced insular cortical thickness may be a biological marker for increased risk of substance dependence.

Cannabis use before age 15 and subsequent executive functioning

Fontes MA1, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, Bressan RA, Lacerda AL.

1. Laboratório Interdisciplinar de Neurociências Clínicas and Unidade de Pesquisas em Álcool e Drogas, Departamento de Psiquiatria, Universidade Federal de São Paulo, São Paulo, Brazil
m.alice@plenamente.com.br

Full text with 46 references

<http://bjp.rcpsych.org/content/198/6/442.long>

Many studies have suggested that adolescence is a period of particular vulnerability to neurocognitive effects associated with substance misuse. However, few large studies have measured differences in cognitive performance between chronic cannabis users who started in early adolescence (before age 15) with those who started later.

We evaluated the performance of 104 chronic cannabis users (49 early-onset users and 55 late-onset users) and 44 controls who undertook neuropsychological tasks, with a focus on executive functioning. Comparisons involving neuropsychological measures were performed using generalised linear model analysis of variance (ANOVA).

The early-onset group showed significantly poorer performance compared with the controls and the late-onset group on tasks assessing sustained attention, impulse control and executive functioning.

Early-onset chronic cannabis users exhibited poorer cognitive performance than controls and late-onset users in executive functioning. Chronic cannabis use, when started before age 15, may have more deleterious effects on neurocognitive functioning.

Expert Review Of Neurotherapeutics • May 2011

THC and CBD oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis

Sastre-Garriga J1, Vila C, Clissold S, Montalban X.

Unitat de Neuroimmunologia Clinica, CEM-Cat, Hospital Universitari Vall d'Hebron (HUVH), Barcelona, Spain
jsastre-garriga@cem-cat.org

<http://www.ncbi.nlm.nih.gov/pubmed/21456949>

People with multiple sclerosis may present with a wide range of disease symptoms during the evolution of the disease; among these, spasticity can have a marked impact on their well-being and quality of life. Symptom control, including spasticity, remains a key management strategy to improve the patient's well-being and functional status. However, available drug therapies for spasticity sometimes have limited benefit and they are often associated with poor tolerability. Sativex is a 1:1 mix of 9-delta-tetrahydrocannabinol and cannabidiol extracted from cloned Cannabis sativa chemovars, which is available as an oromucosal spray. Clinical experience with Sativex in patients with multiple sclerosis is accumulating steadily. Results from randomized, controlled trials have reported a reduction in the severity of symptoms associated with spasticity, leading to a better ability to perform daily activities and an improved perception of patients and their carers regarding functional status when Sativex was added to the current treatment regimen. Adverse events such as dizziness, diarrhea, fatigue, nausea, headache and somnolence occur quite frequently with Sativex, but they are generally of mild-to-moderate intensity and their incidence can be markedly reduced by gradual 'uptitration'. In summary, initial well-controlled studies with Sativex oromucosal spray administered as an add-on to usual therapy have produced promising results and highlight encouraging avenues for future research.

Gut feelings about the endocannabinoid system

Di Marzo V1, Piscitelli F.

1. Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy
vdimarzo@icmib.na.cnr.it

Full text with 57 references

<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2982.2011.01689.x/full>

Stemming from the centuries-old and well known effects of Cannabis on intestinal motility and secretion, research on the role of the endocannabinoid system in gut function and dysfunction has received ever increasing attention since the discovery of the cannabinoid receptors and their endogenous ligands, the endocannabinoids. In this article, some of the most recent developments in this field are discussed, with particular emphasis on new data, most of which are published in *Neurogastroenterology & Motility*, on the potential tonic endocannabinoid control of intestinal motility, the function of cannabinoid type-1 (CB1) receptors in gastric function, visceral pain, inflammation and sepsis, the emerging role of cannabinoid type-2 (CB2) receptors in the gut, and the pharmacology of endocannabinoid-related molecules and plant cannabinoids not necessarily acting via cannabinoid CB1 and CB2 receptors. These novel data highlight the multi-faceted aspects of endocannabinoid function in the GI tract, support the feasibility of the future therapeutic exploitation of this signaling system for the treatment of GI disorders, and leave space for some intriguing new hypotheses on the role of endocannabinoids in the gut.

Journal Of Drug Education • April 2011

Does marijuana use lead to aggression and violent behavior?

By M.K. Ostrowsky

Southern Utah University, Cedar City, UT 84720, USA
Ostrowsky@suu.edu

<http://www.ncbi.nlm.nih.gov/pubmed/22455101>

Marijuana use and violent behavior are causing widespread public concern. This article reviews theory and research on the relation between marijuana use and aggressive/violent behavior. It is evident from the inconsistent findings in the literature that the exact nature of the relation remains unclear. This article identifies several possible reasons for these contradictory findings and provides suggestions for future research. In particular, more research is needed on the different subtypes of aggressive behavior. Further research is also needed to elucidate the associations between gender, marijuana use, and violent behavior. Likewise, an important task for future research is to continue to tease apart the complex relations between gang involvement, marijuana use, and violent behavior. Longitudinal studies also warrant further investigation. Moreover, future research should control for several potentially confounding variables.

Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice

Avraham Y1, Grigoriadis N, Poutahidis T, Vorobiev L, Magen I, Ilan Y, Mechoulam R, Berry E.

1. Department of Human Nutrition and Metabolism, Braun School of Public Health, Hadassah-Hebrew University Medical School, Jerusalem, Israel
yosefa@md.huji.ac.il

Full text with 45 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057300/>

Hepatic encephalopathy is a neuropsychiatric disorder of complex pathogenesis caused by acute or chronic liver failure. We investigated the effects of cannabidiol, a non-psychoactive constituent of *Cannabis sativa* with anti-inflammatory properties that activates the 5-hydroxytryptamine receptor 5-HT(1A), on brain and liver functions in a model of hepatic encephalopathy associated with fulminant hepatic failure induced in mice by thioacetamide. Female Sabra mice were injected with either saline or thioacetamide and were treated with either vehicle or cannabidiol. Neurological and motor functions were evaluated 2 and 3 days, respectively, after induction of hepatic failure, after which brains and livers were removed for histopathological analysis and blood was drawn for analysis of plasma liver enzymes. In a separate group of animals, cognitive function was tested after 8 days and brain 5-HT levels were measured 12 days after induction of hepatic failure. Neurological and cognitive functions were severely impaired in thioacetamide-treated mice and were restored by cannabidiol. Similarly, decreased motor activity in thioacetamide-treated mice was partially restored by cannabidiol. Increased plasma levels of ammonia, bilirubin and liver enzymes, as well as enhanced 5-HT levels in thioacetamide-treated mice were normalized following cannabidiol administration. Likewise, astrogliosis in the brains of thioacetamide-treated mice was moderated after cannabidiol treatment.

Cannabidiol restores liver function, normalizes 5-HT levels and improves brain pathology in accordance with normalization of brain function. Therefore, the effects of cannabidiol may result from a combination of its actions in the liver and brain.

Beneficial effects of cannabinoids (CB) in a murine model of allergen-induced airway inflammation: role of CB1/CB2 receptors

Braun A1, Engel T, Aguilar-Pimentel JA, Zimmer A, Jakob T, Behrendt H, Mempel M.

1. ZAUM - Center for Allergy and Environment, Division of Environmental Dermatology and Allergy
Helmholtz Zentrum München/Technische Universität München (TUM), Ingolstädter Landstrasse 1, 85764 Neuherberg, Germany
andrea.braun@helmholtz-muenchen.de

<http://www.ncbi.nlm.nih.gov/pubmed/21056512>

The endocannabinoid system (ECS) consists of two cannabinoid (CB) receptors, namely CB(1) and CB(2) receptor, and their endogenous (endocannabinoids) and exogenous (cannabinoids, e.g. delta-9-tetrahydrocannabinol (THC)) ligands which bind to these receptors. Based on studies suggesting a role of THC and the ECS in inflammation, the objective of this study was to examine their involvement in type I hypersensitivity using a murine model of allergic airway inflammation. THC treatment of C57BL/6 wildtype mice dramatically reduced airway inflammation as determined by significantly reduced total cell counts in bronchoalveolar lavage (BAL). These effects were greatest when mice were treated during both, the sensitization and the challenge phase. Furthermore, systemic immune responses were significantly suppressed in mice which received THC during sensitization phase. To investigate a role of CB(1/2) receptors in this setting, we used pharmacological blockade of CB(1) and/or CB(2) receptors by the selective antagonists and moreover CB(1)/CB(2) receptor double-knockout mice (CB(1)(-/-)/CB(2)(-/-)) and found neither significant changes in the cell patterns in BAL nor in immunoglobulin levels as compared to wildtype mice. Our results indicate that the activation of the ECS by applying the agonist THC is involved in the development of type I allergies. However, CB(1)/CB(2) receptor-independent signalling seems likely in the observed results.

New York State Dental Journal • April 2011

Significance of cannabis use to dental practice

By W.J. Maloney

New York University College of Dentistry, USA
wjm10@nyu.edu

<http://www.ncbi.nlm.nih.gov/pubmed/21735870>

The illicit use of the three main forms of cannabis-marijuana, hash, hash oil-poses certain obstacles and challenges to the dental professional. There are a number of systemic, as well as oral/head and neck manifestations, associated with cannabis use. Dentists need to be aware of these manifestations in order to take whatever precautions and/or modifications to the proposed treatment that might be necessary.

Central Nervous System Drugs • March 2011

Role of cannabinoids in multiple sclerosis

Zajicek JP1, Apostu VI.

Clinical Neurology Research Group, Peninsula College of Medicine and Dentistry, Plymouth, UK
john.zajicek@phnt.swest.nhs.uk

<http://www.ncbi.nlm.nih.gov/pubmed/21323391>

Although extracts from the cannabis plant have been used medicinally for thousands of years, it is only within the last 2 decades that our understanding of cannabinoid physiology and the provision of evidence for therapeutic benefit of cannabinoids has begun to accumulate. This review provides a background to advances in our understanding of cannabinoid receptors and the endocannabinoid system, and then considers how cannabinoids may help in the management of multiple sclerosis (MS). The relative paucity of treatments for MS-related symptoms has led to experimentation by patients with MS in a number of areas including the use of cannabis extracts. An increasing amount of evidence is now emerging to confirm anecdotal reports of symptomatic improvement, particularly for muscle stiffness and spasms, neuropathic pain and sleep and bladder disturbance, in patients with MS treated with cannabinoids. Trials evaluating a role in treating other symptoms such as tremor and nystagmus have not demonstrated any beneficial effects of cannabinoids. Safety profiles of cannabinoids seem acceptable, although a slow prolonged period of titration improves tolerability. No serious safety concerns have emerged. Methodological issues in trial design and treatment delivery are now being addressed. In addition, recent experimental evidence is beginning to suggest an effect of cannabinoids on more fundamental processes important in MS, with evidence of anti-inflammation, encouragement of remyelination and neuroprotection. Trials are currently under way to test whether cannabinoids may have a longer term role in reducing disability and progression in MS, in addition to symptom amelioration, where indications are being established.

Developmental consequences of perinatal cannabis exposure: behavioral and neuroendocrine effects in adult rodents

Campolongo P1, Trezza V, Ratano P, Palmery M, Cuomo V.

Department of Physiology and Pharmacology, Sapienza University of Rome, P.le A. Moro 5, 00185, Rome, Italy
patrizia.campolongo@uniroma1.it

Full text with 112 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3988409/>

Cannabis is the most commonly used illicit drug among pregnant women. Since the endocannabinoid system plays a crucial role in brain development, maternal exposure to cannabis derivatives might result in long-lasting neurobehavioral abnormalities in the exposed offspring. It is difficult to detect these effects, and their underlying neurobiological mechanisms, in clinical cohorts, because of their intrinsic methodological and interpretative issues.

The present paper reviews relevant rodent studies examining the long-term behavioral consequences of exposure to cannabinoid compounds during pregnancy and/or lactation.

Maternal exposure to even low doses of cannabinoid compounds results in atypical locomotor activity, cognitive impairments, altered emotional behavior, and enhanced sensitivity to drugs of abuse in the adult rodent offspring. Some of the observed behavioral abnormalities might be related to alterations in stress hormone levels induced by maternal cannabis exposure.

There is increasing evidence from animal studies showing that cannabinoid drugs are neuroteratogens which induce enduring neurobehavioral abnormalities in the exposed offspring. Several preclinical findings reviewed in this paper are in line with clinical studies reporting hyperactivity, cognitive impairments and altered emotionality in humans exposed in utero to cannabis. Conversely, genetic, environmental and social factors could also influence the neurobiological effects of early cannabis exposure in humans.

Expert Reviews In Respiratory Medicine • February 2011

Pulmonary effects of marijuana inhalation

Howden ML1, Naughton MT.

Alfred Hospital and Monash University, Prahran 3181, Australia

<http://www.ncbi.nlm.nih.gov/pubmed/21348589>

Marijuana is the most commonly used illicit drug around the world. It is most often consumed through smoking, placing the respiratory system in direct contact with the toxic constituents of the drug, which are similar to those of tobacco cigarettes. However, accurate study of the adverse effects of marijuana is difficult to perform, owing to marijuana's illegal status, variation in smoking technique, often short duration of use compared with tobacco and the frequently confounding factor of concomitant consumption of both marijuana and tobacco. Despite this, there is evidence to suggest that marijuana can impair lung function, damage large airway mucosa and possibly contribute to bullous disease, while its carcinogenic potential is controversial.

Adverse effects of cannabis

<http://www.ncbi.nlm.nih.gov/pubmed/21462790>

Cannabis sativa L., is used to produce a resin that contains high levels of cannabinoids, particularly delta9-tetrahydrocannabinol (THC), which are psychoactive substances. Although cannabis use is illegal in France and in many other countries, it is widely used for its relaxing or euphoric effects, especially by adolescents and young adults. What are the adverse effects of cannabis on health? During consumption? And in the long term? Does cannabis predispose users to the development of psychotic disorders? To answer these questions, we reviewed the available evidence using the standard Prescrire methodology. The long-term adverse effects of cannabis are difficult to evaluate. Since and associated substances, with or without the user's knowledge. Tobacco and alcohol consumption, and particular lifestyles and behaviours are often associated with cannabis use. Some traits predispose individuals to the use of psychoactive substances in general. The effects of cannabis are dose-dependent. The most frequently reported adverse effects are mental slowness, impaired reaction times, and sometimes accentuation of anxiety. Serious psychological disorders have been reported with high levels of intoxication. The relationship between poor school performance and early, regular, and frequent cannabis use seems to be a vicious circle, in which each sustains the other. Many studies have focused on the long-term effects of cannabis on memory, but their results have been inconclusive. There do not * About fifteen longitudinal cohort studies that examined the influence of cannabis on depressive thoughts or suicidal ideation have yielded conflicting results and are inconclusive. Several longitudinal cohort studies have shown a statistical association between psychotic illness and self-reported cannabis use. However, the results are difficult to interpret due to methodological problems, particularly the unknown reliability of self-reported data.

It has not been possible to establish a causal relationship in either direction, because of these methodological limitations. In Australia, the marked increase in cannabis use has not been accompanied by an increased incidence of schizophrenia. On the basis of the available data, we cannot reach firm conclusions on whether or not cannabis use causes psychosis. It seems prudent to inform apparently vulnerable individuals that cannabis may cause acute psychotic decompensation, especially at high doses. Users can feel dependent on cannabis, but this dependence is usually psychological. Withdrawal symptoms tend to occur within 48 hours following cessation of regular cannabis use, and include increased irritability, anxiety, nervousness, restlessness, sleep difficulties and aggression. Symptoms subside within 2 to 12 weeks. Driving under the influence of cannabis doubles the risk of causing a fatal road accident. Alcohol consumption plays an even greater role. A few studies and a number of isolated reports suggest that cannabis has a role in the occurrence of cardiovascular adverse effects, especially in patients with coronary heart disease. Numerous case-control studies have investigated the role of cannabis in the incidence of some types of cancer. Its role has not been ruled out, but it is not possible to determine whether the risk is distinct from that of the tobacco with which it is often smoked. Studies that have examined the influence of cannabis use on the clinical course of hepatitis C are inconclusive. Alcohol remains the main toxic agent that hepatitis C patients should avoid. In practice, the adverse effects of low-level, recreational cannabis use are generally minor, although they can apparently be serious in vulnerable individuals. The adverse effects of cannabis appear overall to be less serious than those of alcohol, in terms of neuropsychological and somatic effects, accidents and violence.

Behavioral Brain Research • December 2010

Functional MRI evidence for inefficient attentional control in adolescent chronic cannabis abuse

Abdullaev Y1, Posner MI, Nunnally R, Dishion TJ.

Child & Family Center, University of Oregon, Eugene, OR 97401, USA
yabdullaev@yahoo.com

<http://www.ncbi.nlm.nih.gov/pubmed/20600341>

Control of attention is a key mechanism underlying behavior regulation. In this study we detail the aspects of attention that covary with the chronic use of cannabis throughout adolescence. We compared performance and brain activation differences in tasks involving attention between young adults with a history of chronic cannabis use during adolescence and matched non-user control subjects. Two tasks were used to activate attention networks: the Attention Network Task (ANT) and the use generation task. In the ANT, chronic users (N=14) differed from controls (N=14) in showing poorer performance (longer reaction time and more errors) on tasks requiring processing of incongruent stimuli reflecting the executive attention network, but not in networks related to alerting or orienting components of attention. Functional MRI of brain activity showed stronger activation within the right prefrontal cortex in chronic users compared to the control group specifically on ANT trials requiring executive attention. The use generation task also revealed significantly stronger activation of the same right prefrontal area in users compared to controls. These results suggest that chronic cannabis users have less efficient executive attention in conflict resolution tasks, demanding more activation in the right prefrontal areas to resolve conflict.

Drugs • December 2010

Role of cannabinoids in the treatment of pain and (painful) spasticity

Karst M1, Wippermann S, Ahrens J.

Department of Anaesthesiology, Pain Clinic, Hannover Medical School, Hannover, Germany
karst.matthias@mh-hannover.de

<http://www.ncbi.nlm.nih.gov/pubmed/21142261>

Both the discovery of the endocannabinoid system (ECS) and its role in the control of pain and habituation to stress, as well as the significant analgesic and antihyperalgesic effects in animal studies, suggest the usefulness of cannabinoids in pain conditions. However, in human experimental or clinical trials, no convincing reduction of acute pain, which may be caused by a nociceptive, ECS-triggered mechanism on the level of the spinal cord, has been demonstrated. In contrast, in chronic pain and (painful) spasticity, an increasing number of randomized, double-blind, placebo-controlled studies have shown the efficacy of cannabinoids, which is combined with a narrow therapeutic index. Patients with unsatisfactory response to other methods of pain therapy and who were characterized by failed stress adaptation particularly benefited from treatment with cannabinoids. None of the attempts to overcome the disadvantage of the narrow therapeutic index, either by changing the route of application or by formulating balanced cannabinoid preparations, have resulted in a major breakthrough. Therefore, different methods of administration and other types of cannabinoids, such as endocannabinoid modulators, should be tested in future trials.

European Journal Of Immunology • December 2010

Cannabinoid receptor activation leads to massive mobilization of myeloid-derived suppressor cells with potent immunosuppressive properties

Hegde VL1, Nagarkatti M, Nagarkatti PS.

Department of Pathology, Microbiology and Immunology, University of South Carolina, School of Medicine, Columbia, SC, USA

Full text with 50 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3076065/>

Cannabinoid receptor activation by agents such as $\Delta(9)$ -tetrahydrocannabinol (THC) is known to trigger immune suppression. Here, we show that administration of THC in mice leads to rapid and massive expansion of CD11b(+)Gr-1(+) myeloid-derived suppressor cells (MDSC) expressing functional arginase and exhibiting potent immunosuppressive properties both in vitro and in vivo. The induction of MDSC by THC was associated with a significant increase in granulocyte CSF. Moreover, administration of anti-granulocyte CSF Ab inhibited the induction of MDSC by THC. THC was able to induce MDSC in TLR4 mutant C3H and C57BL10/ScN mice and hence acted independently of TLR4. Accumulation of MDSC in the periphery with a corresponding decrease in the proportion of CD11b(+)Gr-1(+) cells in the bone marrow, as well as in vivo BrdU labeling and cell-cycle analysis, showed that THC induced mobilization of these cells from bone marrow and their expansion in the periphery. Use of selective antagonists SR141716A and SR144528 against cannabinoid receptors 1 and 2, respectively, as well as receptor-deficient mice showed that induction of MDSC was mediated through activation of both cannabinoid receptors 1 and 2. These studies demonstrate that cannabinoid receptor signaling may play a crucial role in immune regulation via the induction of MDSC.

African Journal Of Psychiatry • Johannesburg • November 2010

**Cannabis use predicts shorter duration of untreated psychosis
and lower levels of negative symptoms in first-episode psychosis: a South African study**

Burns JK1, Jhazbhay K, Emsley R.

1. Department of Psychiatry, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa
burns@ukzn.ac.za

<http://www.ncbi.nlm.nih.gov/pubmed/21390411>

Cannabis use/abuse is a common co-morbid problem in patients experiencing a first episode of psychotic illness (FEP). The relationship between the clinical presentation of FEP and cannabis abuse is complex and warrants further investigation, especially within the South African context.

Current/recent cannabis use was associated with clinical features of psychosis onset that previously have been associated with better outcome. Medium and long-term outcome for cannabis users however, is likely to depend on whether or not cannabis use is ongoing.

Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia

Bosson MG1, Niesink RJ.

Rudolf Magnus Institute of Neuroscience, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

<http://www.ncbi.nlm.nih.gov/pubmed/20624444>

Cannabis use during adolescence increases the risk of developing psychotic disorders later in life. However, the neurobiological processes underlying this relationship are unknown. This review reports the results of a literature search comprising various neurobiological disciplines, ultimately converging into a model that might explain the neurobiology of cannabis-induced schizophrenia. The article briefly reviews current insights into brain development during adolescence. In particular, the role of the excitatory neurotransmitter glutamate in experience-dependent maturation of specific cortical circuitries is examined. The review also covers recent hypotheses regarding disturbances in strengthening and pruning of synaptic connections in the prefrontal cortex, and the link with latent psychotic disorders. In the present model, cannabis-induced schizophrenia is considered to be a distortion of normal late postnatal brain maturation. Distortion of glutamatergic transmission during critical periods may disturb prefrontal neurocircuitry in specific brain areas. Our model postulates that adolescent exposure to Δ^9 -tetrahydrocannabinol (THC), the primary psychoactive substance in cannabis, transiently disturbs physiological control of the endogenous cannabinoid system over glutamate and GABA release. As a result, THC may adversely affect adolescent experience-dependent maturation of neural circuitries within prefrontal cortical areas. Depending on dose, exact time window and duration of exposure, this may ultimately lead to the development of psychosis or schizophrenia. The proposed model provides testable hypotheses which can be addressed in future studies, including animal experiments, reanalysis of existing epidemiological data, and prospective epidemiological studies in which the role of the dose-time-effect relationship should be central.

New High of 46% of Americans Support Legalizing Marijuana

By Elizabeth Mendes

WASHINGTON, D.C. -- While California's marijuana ballot initiative is garnering a lot of attention this election cycle, Gallup finds that nationally, a new high of 46% of Americans are in favor of legalizing use of the drug, and a new low of 50% are opposed. The increase in support this year from 44% in 2009 is not statistically significant, but is a continuation of the upward trend seen since 2000.

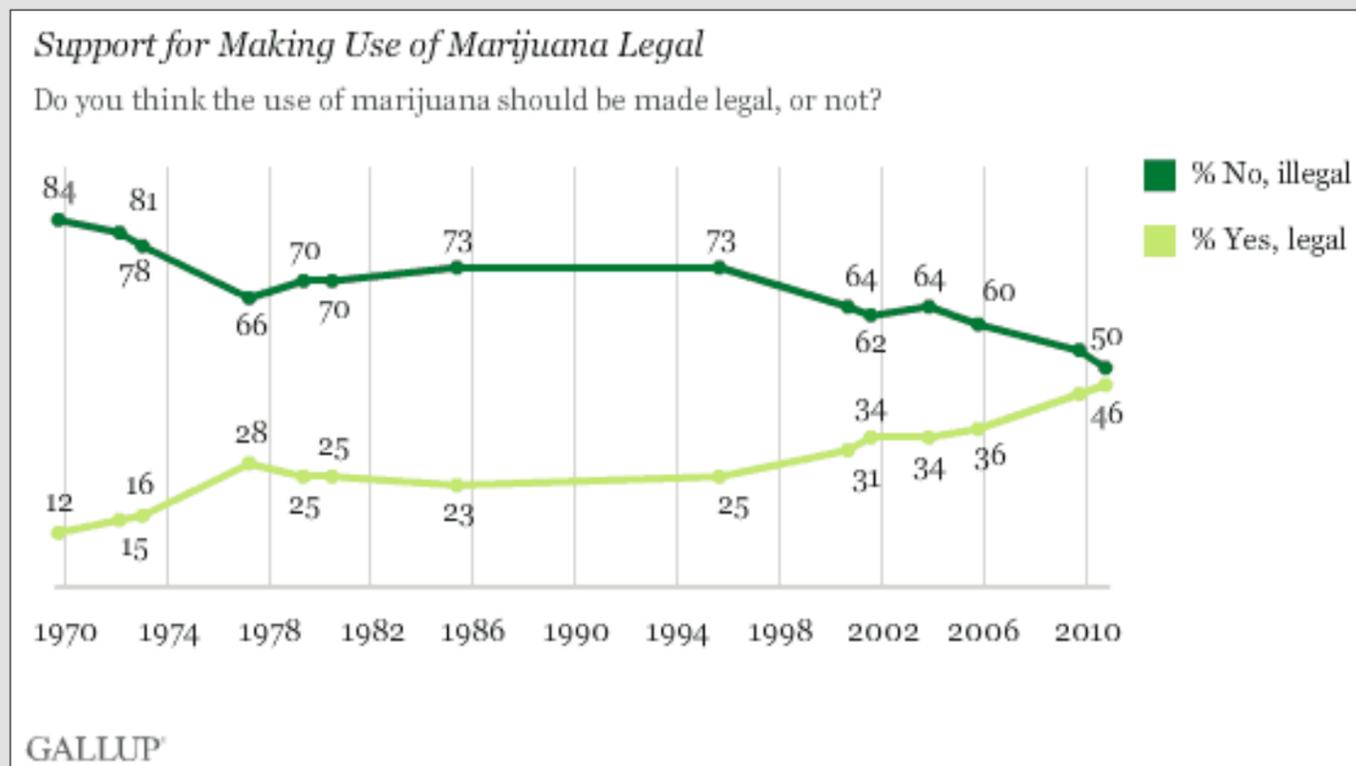
reduce pain and suffering. This figure is down, however, from 78% in 2005 and 75% in 2003.

Across numerous subgroups, liberals' support, at 72%, is by far the highest. There is widespread support for legalization among 18- to 29-year-olds (61%) as well. Majority support is also found among Democrats, independents, men, and political moderates.

These results are from Gallup's annual Crime poll, conducted Oct. 7-10. Approximately 8 in 10 Americans were opposed to legalizing marijuana when Gallup began asking about it in the late 1960s and early 1970s. Support for legalizing the drug jumped to 31% in 2000 after holding in the 25% range from the late 1970s to the mid-1990s.

A separate question in the poll asked about legalizing marijuana for medical use, and found support significantly higher than it is for legalizing the use of marijuana in general. Seventy percent of Americans say they favor making marijuana legally available for doctors to prescribe in order to

political, and ideological differences in support are much the same as they were in 2009.



A large majority of those living in the West, which encompasses California, are in favor of making the drug legal. Support is significantly lower in the South and Midwest. Political conservatives and Republicans are the least supportive of legalizing marijuana. Seniors express a similarly low level of support.

Women are 10 percentage points less likely than men to favor legalizing the drug. These demographic,

Arguments for and against legalizing marijuana -- for personal or medical use -- are likely to continue for years to come. Even if Proposition 19 wins in California on Nov. 2, as state law it will still come up against federal law, which bans the growth and sale of marijuana.

Support for making the drug legal in general, however, is growing among Americans. The public is almost evenly split this year, with 46% in favor and 50% opposed. If the trend of the past decade continues at a similar pace, majority support could be a reality within the next few years.

Results for this Gallup poll are based on telephone interviews conducted Oct. 7-10, 2010, with a random sample of 1,025 adults, aged 18 and older, living in the continental U.S., selected using random-digit-dial sampling.

Each question reported here was asked of a half-sample of approximately 500 national adults.

For results based on these total samples of nation-

*Support for Legalizing Use of Marijuana,
by Subgroup*

Oct. 7-10, 2010

	% Yes, legal
Liberal	72
18 to 29	61
West	58
Democrat	55
Independent	54
Men	51
Moderate	51
30 to 49	49
East	47
50 to 64	43
Midwest	42
Women	41
South	40
65 and older	32
Conservative	30
Republican	29

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al adults, one can say with 95% confidence that the maximum margin of sampling error is ± 5 percentage points. Interviews are conducted with respondents on landline telephones (for respondents with a landline telephone) and cellular phones (for respondents who are cell phone-only). Each sample includes a minimum quota of 150 cell phone-only respondents and 850 landline respondents, with additional minimum quotas among landline respondents for gender within region. Landline respondents are chosen at random within each household on the basis of which member had the most recent birthday.

Samples are weighted by gender, age, race, education, region, and phone lines. Demographic weighting targets are based on the March 2009 Current Population Survey figures for the aged 18 and older non-institutionalized population living in continental U.S. telephone households. All reported margins of sampling error include the computed design effects for weighting and sample design. In addition to sampling error, question wording and practical difficulties in conducting surveys can introduce error or bias into the findings of public opinion polls.

Grants
**Medical Marijuana Policy Research:
Exploring Trends and Impacts**

Full text

www.grants.nih.gov/grrfa-files/RFA-DA-11-008.html

Since 1996, 15 states in the U.S. have passed laws to decriminalize the use of medical marijuana in some form and other states are now considering similar changes. Little is known about the effects of changing state and local laws, regulations, and policies on the epidemiology of cannabis or other drug use. This FOA will support research on medical marijuana-related “quasi-natural experiments” in the US. It solicits Research Project Grant (R01) applications to assess social, behavioral, and public health impacts of medical marijuana use and policies. Secondary data applications which utilize national or state level longitudinal or panel data are highly encouraged.

Section I. Funding Opportunity Description

Purpose and Objectives. This FOA, issued by the National Institute on Drug Abuse (NIDA), solicits Research Project Grant (R01) applications from institutions/organizations that propose research on medical marijuana-related “quasi-natural experiments” in the US to understand the effects of changing local laws, regulations and policies on the epidemiology of cannabis or other drug and alcohol use including the use of tobacco. These quasi-natural experiments may utilize a community or other population-level law, regulation, or public policy intervention that affects medical marijuana use (i.e. decriminalization, etc.). To address this objective, applicants should propose research studies that will assess social, behavioral, and public health impacts of medical marijuana use and policies. The results of research supported by this FOA are expected to provide critical epidemiologic and eval-

uation data to inform local, regional, and national public policy and public health research relevant to marijuana use across the Nation.

Background. Since 1996, 15 states in the U.S. have passed laws to decriminalize the use of medical marijuana in some form and other states are now considering similar changes. A great deal of heterogeneity exists among states regarding implementation and regulation of medical marijuana, including zoning regulations on numbers and locations of dispensaries; licensing of dispensaries; prescriber practices and compliance monitoring; identification systems for patients to obtain medical marijuana; inspections and oversight of cultivation; price and purity medical marijuana requirements; wait lists to accommodate patient demand for prescriptions; prescriber licensing; law enforcement policies and personnel to enforce restrictions on sales; and insurance regulations and requirements for cases of medical malpractice, prescription fraud, product contamination, adverse reactions, etc.

Though drug abuse research has focused largely on individual risk factors, the universe of determinants includes many levels outside of the individual—including family, neighborhood, community, population-specific, economic and societal factors. Several decades of research have shown that social environment factors are strongly and consistently related to the development of behavioral risk factors and to the development, progression, and outcomes of drug abuse and HIV/AIDS and other infectious diseases. This FOA represents a unique opportunity to spur critical research on the

effects of and attitudes surrounding medical marijuana laws, regulations, and policies as they are rapidly evolving.

Research topics that fall within the scope of this FOA include but are not limited to the following:

Epidemiologic research on the prevalence, incidence, patterns, and emerging trends in the varying medical marijuana policy environment across states or localities, or before and after law, regulation, or policy change. Studies of the effects of medical marijuana laws, regulations, and policies on key health and social indicators, such as rates of use of other drugs, tobacco, and alcohol, rates of corollary risk and protective health behaviors; sexually transmitted infections and HIV; substance abuse treatment admission; truancy, academic performance, school dropout; arrests for drug buying or selling, criminality, accidents associated with drugged driving; and employment outcomes. Research to explore the impact of medical marijuana laws, regulations, and policies in the context of HIV/AIDS, including the use of medical marijuana among people living with HIV and its effects on health, decision making, adherence to HAART and retention in HIV care, and risky sexual behaviors.

Research to understand the effects of medical marijuana laws, regulations, and policies on social norms, attitudes, beliefs, perceptions of harm and disapproval, and drug use behaviors of youth, adults, and parents in communities where the laws have changed, or who live with family members who use medical marijuana, or who have friends who use nonmedical marijuana and other drugs. Studies exploring how changes in norms influence epidemiologic trends are also of interest.

Studies investigating how changes in medical marijuana supply and demand may influence drug abuse through changes in price, purity, availability and other market dynamics.

Studies examining the moderating or mediating effects of medical marijuana laws, regulations and policies on existing prevention interventions or youth drug use and drug problems in the context of prevention interventions.

Research examining youth access to and opportunities to obtain and use marijuana in communities that adopt laws, regulations and policies decriminalizing medical marijuana use versus communities that do not adopt them and studies investigating family and other social environmental factors that influence access and opportunities to obtain marijuana.

Also encouraged are applications that utilize the following: (a) national or state level longitudinal or panel secondary data, (b) systems science methodologies (e.g., Agent Based Modeling; System Dynamics modeling, Network Analysis), (c) geographic information systems (GIS), (d) multi-method research approaches (combinations of qualitative, ethnographic, observational, and quantitative), or (e) research using advanced statistical methods that support causal inferences.

Research studies solely using non-United States data, analyses of cross-sectional data consisting of only a single point in time, Phase III clinical trials, or intervention effectiveness studies will not be considered responsive to this FOA. Inclusion of international data for comparison purposes to United States data is acceptable.

Hippocampus • October 2010

Cannabinoids modulate hippocampal memory and plasticity

Abush H1, Akirav I.

Department of Psychology, University of Haifa, Haifa, Israel

<http://www.ncbi.nlm.nih.gov/pubmed/6090910>

Considerable evidence demonstrates that cannabinoid agonists impair whereas cannabinoid antagonists improve memory and plasticity. However, recent studies suggest that the effects of cannabinoids on learning do not necessarily follow these simple patterns, particularly when emotional memory processes are involved.

Our findings suggest diverse effects of the cannabinoid system on CA1 memory and plasticity that cannot be categorized simply into an impairing or an enhancing effect of cannabinoid activation and deactivation, respectively. Moreover, they provide preclinical support for the suggestion that targeting the endocannabinoid system may aid in the treatment of disorders associated with impaired extinction-like processes, such as post-traumatic stress disorder.

Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]

Morgan CJ1, Schafer G, Freeman TP, Curran HV.

Clinical Psychopharmacology Unit, University College London, Gower St, London WC1E 6BT, UK

Full text, PDF, with 35 references

<http://bjp.rcpsych.org/content/bjprcpsych/197/4/285.full.pdf>

The two main constituents of cannabis, cannabidiol and $\Delta(9)$ -tetrahydrocannabinol (THC), have opposing effects both pharmacologically and behaviourally when administered in the laboratory. Street cannabis is known to contain varying levels of each cannabinoid.

Cannabis users (n = 134) were tested 7 days apart on measures of memory and psychotomimetic symptoms, once while they were drug free and once while acutely intoxicated by their own chosen smoked cannabis. Using an unprecedented methodology, a sample of cannabis (as well as saliva) was collected from each user and analysed for levels of cannabinoids. On the basis of highest and lowest cannabidiol content of cannabis, two groups of individuals were directly compared.

Groups did not differ in the THC content of the cannabis they smoked. Unlike the marked impairment in prose recall of individuals who smoked cannabis low in cannabidiol, participants smoking cannabis high in cannabidiol showed no memory impairment. Cannabidiol content did not affect psychotomimetic symptoms, which were elevated in both groups when intoxicated.

The antagonistic effects of cannabidiol at the CB(1) receptor are probably responsible for its profile in smoked cannabis, attenuating the memory-impairing effects of THC. In terms of harm reduction, users should be made aware of the higher risk of memory impairment associated with smoking low-cannabidiol strains of cannabis like 'skunk' and encouraged to use strains containing higher levels of cannabidiol.

Structural MRI findings in long-term cannabis users: what do we know?

Lorenzetti V1, Lubman DI, Whittle S, Solowij N, Yücel M.

Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Victoria, Australia

<http://www.ncbi.nlm.nih.gov/pubmed/20590400>

In animal studies, tetrahydrocannabinol (THC) has been found to affect brain morphology, particularly within areas rich in cannabinoid receptors (e.g., hippocampus, cerebral cortex). While cannabis remains the most widely used illicit drug worldwide, there has been limited work investigating its effects on human brain tissue. In this paper, we conducted a systematic review of existing structural magnetic resonance imaging studies to examine whether cannabis use is associated with significant changes in brain anatomy. We identified only 13 structural neuroimaging studies, which were diverse in terms of sample characteristics (e.g., age of participants, duration and frequency of use) and methodology (e.g., image analysis). No study found global structural changes in cannabis users, although six studies reported regional alterations. While changes in the hippocampus and parahippocampus were frequently identified, the findings were inconsistent across studies. The available literature also provides some evidence that regional structural changes are associated with cannabis use patterns (particularly cumulative dosage and frequency of use), as well as measures of psychopathology (e.g., measures of depressive and psychotic symptoms). Together, these structural imaging findings suggest that THC exposure does affect brain morphology, especially in medial-temporal regions. Given the small literature available and the limitations of studies to date, further research is clearly required, particularly given the prevalence of cannabis use worldwide.

Potency trends of Δ 9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008

Mehmedic Z1, Chandra S, Slade D, Denham H, Foster S, Patel AS, Ross SA, Khan IA, ElSohly MA.

1. National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University, MS 38677, USA

<http://www.ncbi.nlm.nih.gov/pubmed/20487147>

The University of Mississippi has a contract with the National Institute on Drug Abuse (NIDA) to carry out a variety of research activities dealing with cannabis, including the Potency Monitoring (PM) program, which provides analytical potency data on cannabis preparations confiscated in the United States. This report provides data on 46,211 samples seized and analyzed by gas chromatography-flame ionization detection (GC-FID) during 1993-2008. The data showed an upward trend in the mean Δ (9)-tetrahydrocannabinol (Δ (9)-THC) content of all confiscated cannabis preparations, which increased from 3.4% in 1993 to 8.8% in 2008. Hashish potencies did not increase consistently during this period; however, the mean yearly potency varied from 2.5-9.2% (1993-2003) to 12.0-29.3% (2004-2008). Hash oil potencies also varied considerably during this period ($16.8 \pm 16.3\%$). The increase in cannabis preparation potency is mainly due to the increase in the potency of nondomestic versus domestic samples.

The influence of recency of use on fMRI response during spatial working memory in adolescent marijuana users

Schweinsburg AD1, Schweinsburg BC, Medina KL, McQueeny T, Brown SA, Tapert SF.

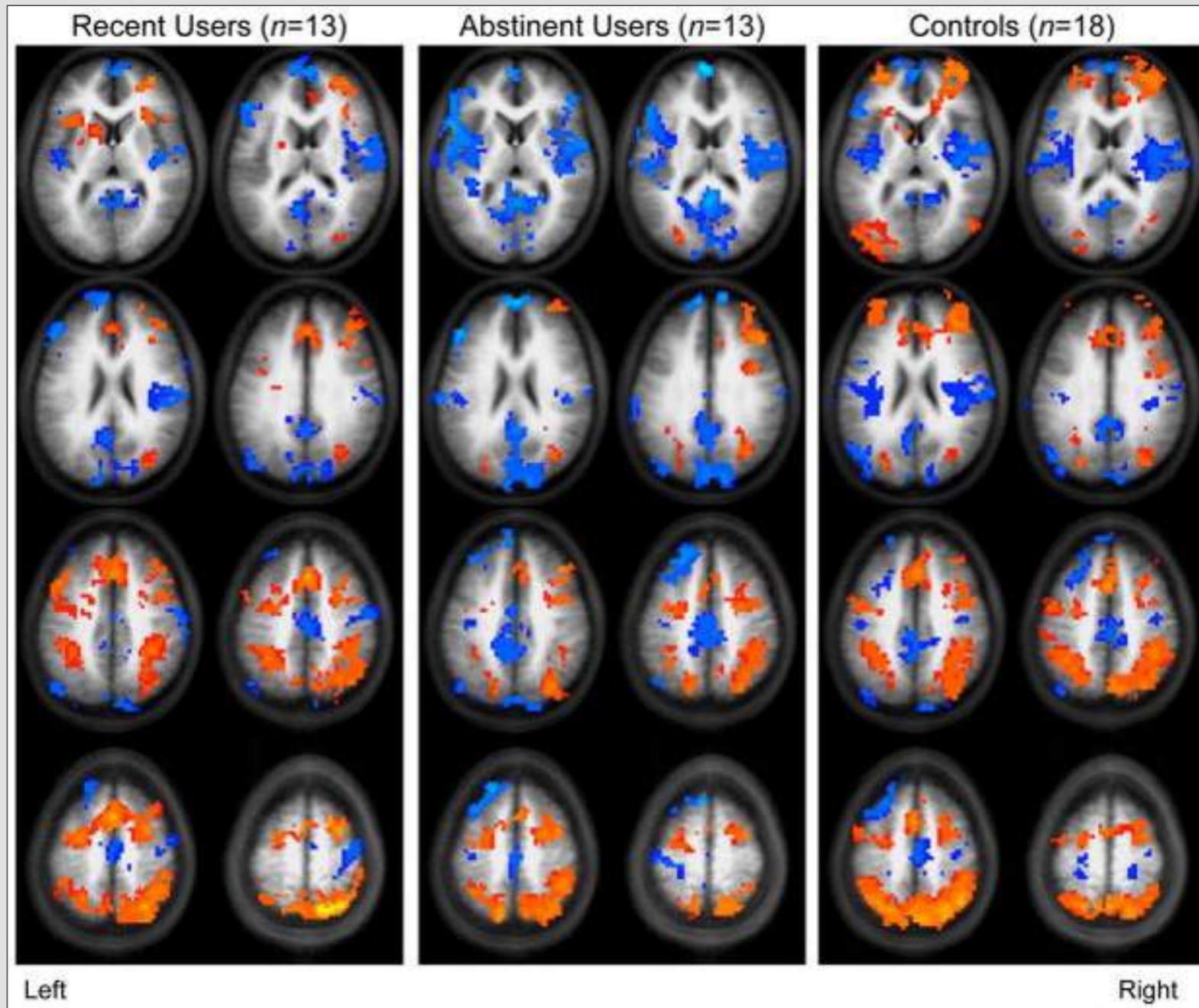
1. Yale University, Department of Psychiatry, New Haven, CT, USA

Full text with 77 references

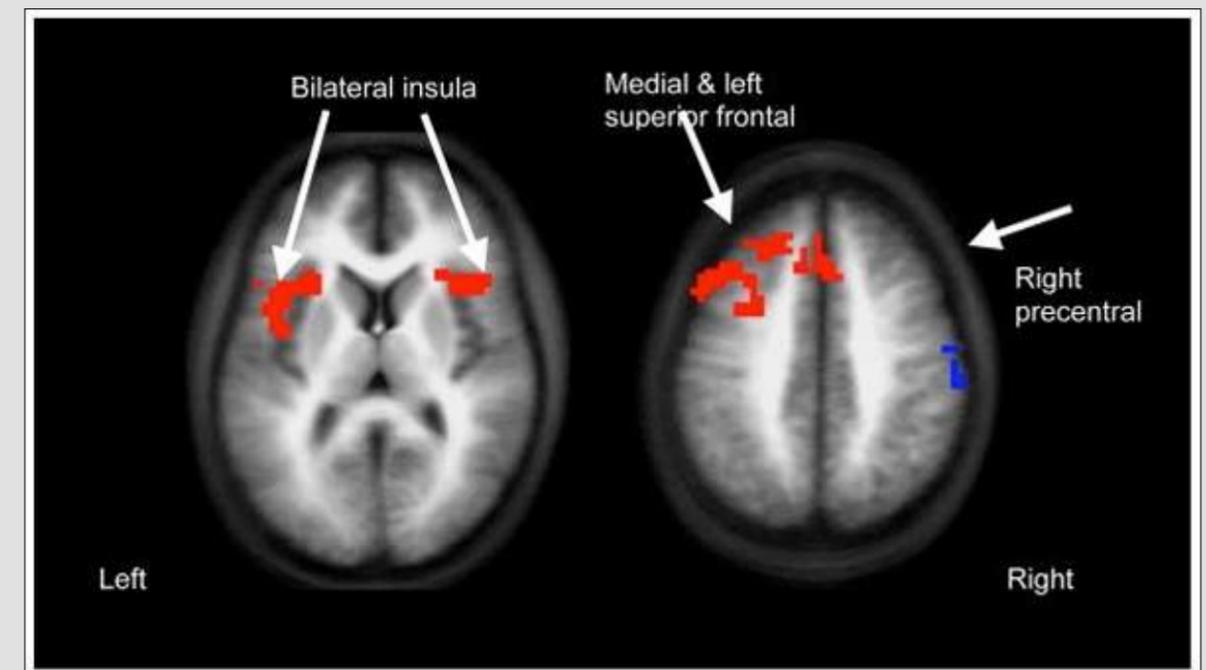
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3016644/>

Some neurocognitive recovery occurs within a month of abstinence from heavy marijuana use, yet functional magnetic resonance imaging (fMRI) has revealed altered activation among recent and abstinent adult users. We compared fMRI response during a spatial working memory (SWM) task between adolescent marijuana users with brief and sustained durations of abstinence. Participants were 13 recent users (two to seven days abstinent), 13 abstinent users (27 to 60 days abstinent), and 18 non-using controls, all ages 15 to 18. Groups were similar on demographics, had no psychiatric or medical disorders, and user groups were similar on substance histories. Teens performed a two-back SWM task during fMRI. Recent users showed greater fMRI response in medial and left superior prefrontal cortices, as well as bilateral insula. Abstinent users had increased response in the right precentral gyrus (clusters ≥ 1328 microl, $p < .05$). Results suggest that adolescents who recently used marijuana show increased brain activity in regions associated with working memory updating and inhibition. This study preliminarily suggests that (1) recent marijuana use may disrupt neural connections associated with SWM and result in compensatory brain response, and (2) sustained abstinence from marijuana may be associated with improvements in SWM response among adolescents.

fMRI images and study design schematic on following pages

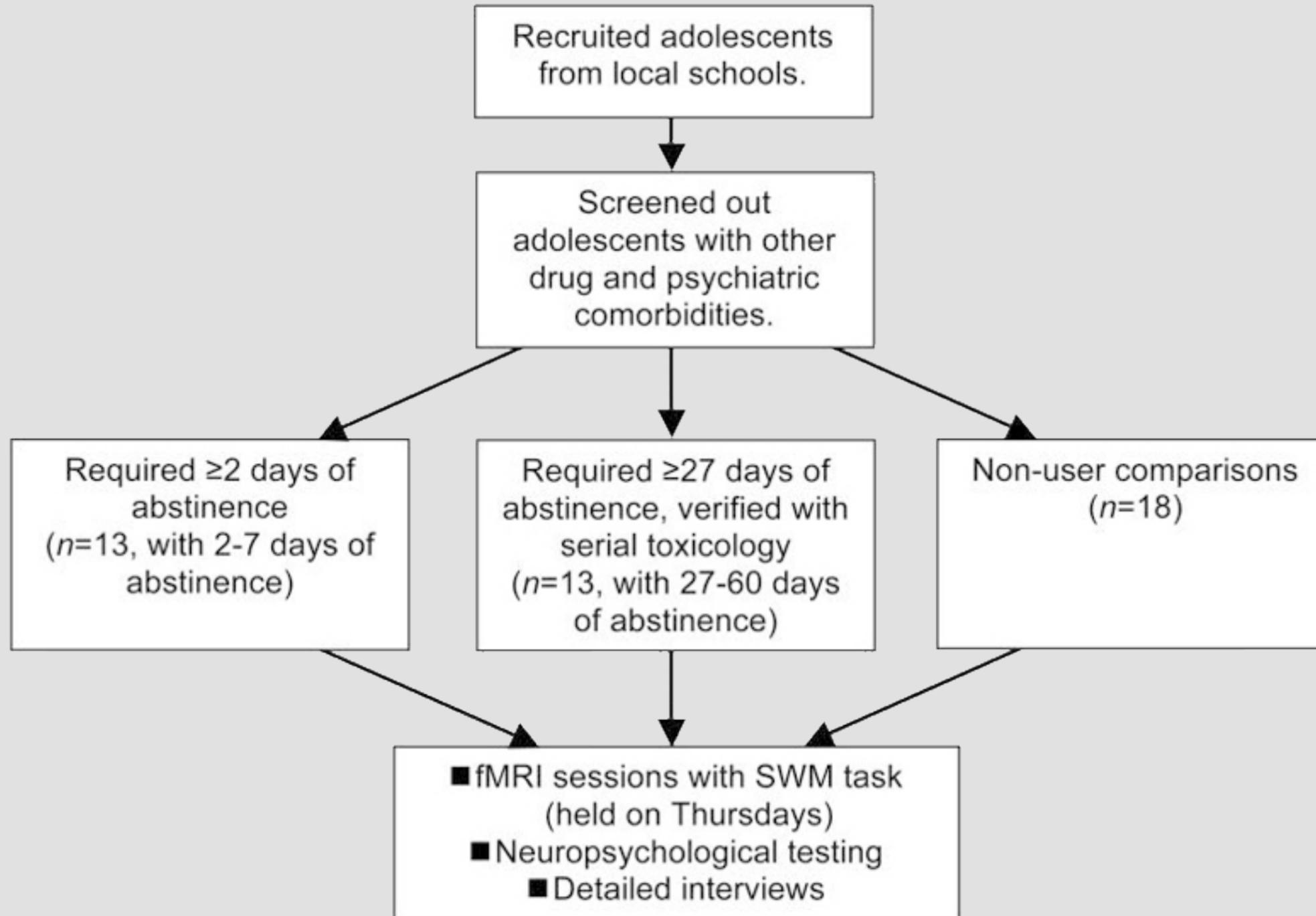


BOLD response to spatial working memory relative to vigilance in recent marijuana users, abstinent marijuana users, and non-using controls. Activation maps represent regions of significantly greater response to the spatial working memory relative to the vigilance trials (orange colors), and greater response to vigilance relative to spatial working memory trials (blue) as determined by single sample t-tests ($p < .05$, corrected for multiple comparisons; clusters > 49 contiguous voxels each activated at $p < .05$). Activations are displayed on top of an averaged anatomical image.



Activation maps showing significant group differences in spatial working memory BOLD response between adolescent marijuana users with recent use ($n=13$) compared to adolescents with sustained abstinence ($n=13$). Activations are displayed on an averaged anatomical image. Activation maps are thresholded at an overall $p < .05$ for the whole brain, corrected for multiple comparisons ($p < .05$, cluster volume ≥ 1328 microliters). Red indicates clusters in which Recent Users showed more brain response than Abstinent Users during spatial working memory; blue indicates clusters in which Abstinent Users showed more response than Recent Users during the simple vigilance control condition.

Study Design



Fitoterapia • July 2010

Characterization and antimicrobial activity of essential oils of industrial hemp varieties (*Cannabis sativa* L.)

Nissen L1, Zatta A, Stefanini I, Grandi S, Sgorbati B, Biavati B, Monti A.

1. Microbiology Area, DiSTA (Department of Agroenvironmental Sciences and Technologies), Italy
lorenzo.nissen@unibo.it

<http://www.ncbi.nlm.nih.gov/pubmed/19969046>

The present study focused on inhibitory activity of freshly extracted essential oils from three legal (THC<0.2% w/v) hemp varieties (Carmagnola, Fibranova and Futura) on microbial growth. The effect of different sowing times on oil composition and biological activity was also evaluated. Essential oils were distilled and then characterized through the gas chromatography and gas chromatography-mass spectrometry. Thereafter, the oils were compared to standard reagents on a broad range inhibition of microbial growth via minimum inhibitory concentration (MIC) assay. Microbial strains were divided into three groups: i) Gram (+) bacteria, which regard to food-borne pathogens or gastrointestinal bacteria, ii) Gram (-) bacteria and iii) yeasts, both being involved in plant interactions. The results showed that essential oils of industrial hemp can significantly inhibit the microbial growth, to an extent depending on variety and sowing time. It can be concluded that essential oils of industrial hemp, especially those of Futura, may have interesting applications to control spoilage and food-borne pathogens and phytopathogens microorganisms.

When Cannabis Is Available and Visible at School—A Multilevel Analysis of Students' Cannabis Use

By Emmanuel Kuntsche

<http://eric.ed.gov/?id=EJ902759>

Aims: To investigate the links between the visibility of cannabis use in school (measured by teachers' reports of students being under the influence of cannabis on school premises), the proportion of cannabis users in the class, perceived availability of cannabis, as well as adolescent cannabis use.

A multilevel regression model was estimated based on a Swiss national representative sample of 5935 students in the 8th and 9th grades (mean age=14.8, SD=0.9) and their 343 teachers.

The visibility of cannabis use in school was related to the students' own cannabis use, even when the proportion of cannabis users in the class was taken into account. In addition, the strength of the association between perceived availability and students' cannabis use increased as the visibility of cannabis use in school became higher.

Visible cannabis use at school appears to trigger cannabis use among students, e.g. by raising the degree to which they perceive its ready availability. Teachers, school authorities, and policy-makers must assume responsibility for creating a more protective school environment, by establishing and enforcing school regulations for example.

Analytical characterization of Hempseed (seed of *Cannabis sativa* L.) oil from eight regions in China

Chen T1, He J, Zhang J, Zhang H, Qian P, Hao J, Li L.

Research Center of China-Hemp Materials of The Quartermaster Research Institute of the General Logistic Department, Beijing, China

<http://www.ncbi.nlm.nih.gov/pubmed/22435611>

In this study, eight cultivars of hempseed were collected from different regions of China for analysis of physiochemical properties and chemical composition, as well as for seed indexes and proximate composition of seed kernel. The results indicated that Yunma No. 1 and Bama Huoma, with more than 50% oil and 30% protein in dehulled seed, could be considered as oil extraction material and protein source with respect to kernel yield. Iodine values ranging from 153.6 to 169.1 g/100 g reflected the high degree of unsaturation. The concentration of unsaturated fatty acids exceeded 90%, higher than most conventional vegetable oils. Moreover, polyunsaturated fatty acids ranged from 76.26% to 82.75% and were mainly composed of linoleic acid and α -linolenic acid with a ratio close to 3:1. γ -Tocopherol was found at an average concentration of 28.23 mg/100 g of hempseed oil. The results indicated that hempseed oil is a potentially valuable vegetable oil.

Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models

Malone DT1, Hill MN, Rubino T.

1. Medicinal Chemistry and Drug Action, Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Vic., Australia

Full text with 165 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931552/>

Cannabis is one of the most widely used illicit drugs among adolescents, and most users first experiment with it in adolescence. Adolescence is a critical phase for brain development, characterized by neuronal maturation and rearrangement processes, such as myelination, synaptic pruning and dendritic plasticity.

The endocannabinoid system plays an important role in fundamental brain developmental processes such as neuronal cell proliferation, migration and differentiation. Therefore changes in endocannabinoid activity during this specific developmental phase, induced by the psychoactive component of marijuana, Delta(9)-tetrahydrocannabinol, might lead to subtle but lasting neurobiological changes that can affect brain functions and behaviour. In this review, we outline recent research into the endocannabinoid system focusing on the relationships between adolescent exposure to cannabinoids and increased risk for certain neuropsychiatric diseases such as schizophrenia, as highlighted by both human and animal studies.

Particular emphasis will be given to the possible mechanisms by which adolescent cannabis consumption could render a person more susceptible to developing psychoses such as schizophrenia.

Cannabinoids and the gut: new developments and emerging concepts

Izzo AA1, Sharkey KA.

1. Department of Experimental Pharmacology, University of Naples Federico II and Endocannabinoid Research Group, Naples, Italy
aaizzo@unina.it

<http://www.ncbi.nlm.nih.gov/pubmed/20117132>

Cannabis has been used to treat gastrointestinal (GI) conditions that range from enteric infections and inflammatory conditions to disorders of motility, emesis and abdominal pain. The mechanistic basis of these treatments emerged after the discovery of Delta(9)-tetrahydrocannabinol as the major constituent of Cannabis. Further progress was made when the receptors for Delta(9)-tetrahydrocannabinol were identified as part of an endocannabinoid system, that consists of specific cannabinoid receptors, endogenous ligands and their biosynthetic and degradative enzymes. Anatomical, physiological and pharmacological studies have shown that the endocannabinoid system is widely distributed throughout the gut, with regional variation and organ-specific actions. It is involved in the regulation of food intake, nausea and emesis, gastric secretion and gastroprotection, GI motility, ion transport, visceral sensation, intestinal inflammation and cell proliferation in the gut. Cellular targets have been defined that include the enteric nervous system, epithelial and immune cells. Molecular targets of the endocannabinoid system include, in addition to the cannabinoid receptors, transient receptor potential vanilloid 1 receptors, peroxisome proliferator-activated receptor alpha receptors and the orphan G-protein coupled receptors, GPR55 and GPR119. Pharmacological agents that act on these targets have been shown in preclinical models to have therapeutic potential. Here, we discuss cannabinoid receptors and their localization in the gut, the proteins involved in endocannabinoid synthesis and degradation and the presence of endocannabinoids in the gut in health and disease. We focus on the pharmacological actions of cannabinoids in relation to GI disorders, highlighting recent data on genetic mutations in the endocannabinoid system in GI disease.

Cannabis-induced cerebral and myocardial infarction in a young woman

Duchene C1, Olindo S, Chausson N, Jeannin S, Cohen-Tenoudji P, Smadja D.

1. Service de Neurologie, CHU Pierre-Zobda-Quitman, La Meynard, 97200 Fort-de-France, Martinique, France

<http://www.ncbi.nlm.nih.gov/pubmed/20005549>

Cannabis is the most consumed drug in the world particularly in young adults. Few reports have suggested a causal role of cannabis in the development of cerebral or cardiovascular events. We describe the first association of myocardial infarction and stroke after heavy cannabis consumption in a 45-year-old woman.

Stroke occurred in relation with a right carotid and middle cerebral artery thrombosis after cannabis abuse. The patient was successfully treated with intravenous rt-PA. Two days after her admission, she presented a myocardial infarction due to a coronary thrombosis. Cerebral and coronary arteries were angiographically normal. Etiological tests were negative and a toxic cause in relation with cannabis consumption was concluded.

Cannabis can be associated with vascular events by different mechanisms. Thrombosis may occur in cerebral and/or coronary arteries. We suggest that it might be useful to search for cannabis consumption systematically in young subjects victims of stroke and myocardial infarction.

Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use

Mata I1, Perez-Iglesias R, Roiz-Santiañez R, Tordesillas-Gutierrez D, Pazos A, Gutierrez A, Vazquez-Barquero JL, Crespo-Facorro B.

Department of Psychiatry, University Hospital Marques de Valdecilla, School of Medicine, University of Cantabria, IFIMAV, Santander, Spain

<http://www.ncbi.nlm.nih.gov/pubmed/20045399>

Although cannabis is the most widely used illicit drug in the world, the long-term effect of its use in the brain remains controversial. In order to determine whether adolescence and early-adulthood cannabis use is associated with gross volumetric and gyrification abnormalities in the brain, we set up a cross-sectional study using structural magnetic resonance imaging in a sample of general population subjects. Thirty cannabis-using subjects (mean age, 25.7 years; mean duration of regular use, 8.4 years, range: 3-21) with no history of polydrug use or neurologic/mental disorder and 44 non-using control subjects (mean age, 25.8 years) were included. Cannabis users showed bilaterally decreased concavity of the sulci and thinner sulci in the right frontal lobe. Among non-users, age was significantly correlated with decreased gyrification (i.e., less concave sulci and more convex gyri) and decreased cortical thickness, supporting the notion of age-related gyrification changes. However, among cannabis users gyrification indices did not show significant dependency on age, age of regular cannabis use initiation, or cumulative exposure to cannabis. These results suggest that cannabis use in adolescence and early-adulthood might involve a premature alteration in cortical gyrification similar to what is normally observed at a later age, probably through disruption of normal neurodevelopment.

Psychological Medicine • March 2010

Neuroimaging in cannabis use: a systematic review of the literature

Martín-Santos R1, Fagundo AB, Crippa JA, Atakan Z, Bhattacharyya S, Allen P, Fusar-Poli P, Borgwardt S, Seal M, Busatto GF, McGuire P.

Section of Neuroimaging, PO67 Division of Psychological Medicine, Institute of Psychiatry, King's College London, UK
rmsantos@clinic.ub.es

<http://www.ncbi.nlm.nih.gov/pubmed/19627647>

We conducted a systematic review to assess the evidence for specific effects of cannabis on brain structure and function. The review focuses on the cognitive changes associated with acute and chronic use of the drug.

Functional neuroimaging studies suggest a modulation of global and prefrontal metabolism both during the resting state and after the administration of THC/marijuana cigarettes. Minimal evidence of major effects of cannabis on brain structure has been reported.

Sex differences in the effects of marijuana on simulated driving performance

Anderson BM1, Rizzo M, Block RI, Pearlson GD, O'Leary DS.

1. Olin Neuropsychiatry Research Center, 200 Retreat Avenue - Whitehall Bldg, Hartford Hospital Institute of Living, Hartford, CT 06106, USA
dr.beth.anderson@gmail.com

Full text with 63 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3033009/>

In the United States, one in six teenagers has driven under the influence of marijuana. Driving under the influence of marijuana and alcohol is equally prevalent, despite the fact that marijuana use is less common than alcohol use. Much of the research examining the effects of marijuana on driving performance was conducted in the 1970s and led to equivocal findings. During that time, few studies included women and driving simulators were rudimentary. Further, the potency of marijuana commonly used recreationally has increased. This study examined sex differences in the acute effects of marijuana on driving performance using a realistic, validated driving simulator. Eighty-five subjects (n = 50 males, 35 females) participated in this between-subjects, double-blind, placebo controlled study. In addition to an uneventful, baseline segment of driving, participants were challenged with collision avoidance and distracted driving scenarios. Under the influence of marijuana, participants decreased their speed and failed to show expected practice effects during a distracted drive. No differences were found during the baseline driving segment or collision avoidance scenarios. No differences attributable to sex were observed. This study enhances the current literature by identifying distracted driving and the integration of prior experience as particularly problematic under the influence of marijuana.



View of the Simulator for Interdisciplinary Research in Ergonomics and Neuroscience (SIREN)
Cab and Front Screens - SIREN is a realistic, validated driving simulator

Opposite Effects of Δ -9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology

Sagnik Bhattacharyya,^{1,*} Paul D Morrison,² Paolo Fusar-Poli,^{1,3} Rocio Martin-Santos,^{1,4} Stefan Borgwardt,^{1,5} Toby Winton-Brown,¹ Chiara Nosarti,⁶ Colin M O'Carroll,⁷ Marc Seal,⁸ Paul Allen,¹ Mitul A Mehta,⁹ James M Stone,¹ Nigel Tunstall,² Vincent Giampietro,¹⁰ Shitij Kapur,¹¹ Robin M Murray,² Antonio W Zuardi,^{12,13} José A Crippa,^{12,13} Zerrin Atakan,¹ and Philip K McGuire¹

1. Section of Neuroimaging, Division of Psychological Medicine & Psychiatry, Institute of Psychiatry, King's College London, London, UK
2. Division of Psychological Medicine & Psychiatry, Institute of Psychiatry, King's College London, London, UK
3. Section of Psychiatry, Department of Health Sciences, University of Pavia, Pavia, Italy
4. Department of Psychiatry, Institut of Neurosciences, Hospital Clínic, Barcelona, Spain
5. Psychiatric Outpatient Department, University Hospital Basel, Basel, Switzerland
6. Cognition Schizophrenia and Imaging (CSI) Laboratory, Division of Psychological Medicine & Psychiatry, Institute of Psychiatry, King's College London, London, UK
7. Columbia University, Department of Neuroscience, New York, NY, USA
8. Melbourne Neuropsychiatry Centre, The University of Melbourne, National Neuroscience Facility, Carlton South, VIC, Australia
9. Centre for Neuroimaging Sciences, Institute of Psychiatry, KCL, London, UK
10. Department of Biostatistics, Institute of Psychiatry, King's College London, London, UK
11. Section on Schizophrenia, Imaging and Therapeutics, Division of Psychological Medicine & Psychiatry, Institute of Psychiatry, King's College London, London, UK
12. Department of Neuroscience and Behavior, Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil
13. INCT Translational Medicine, Ribeirão Preto, Brazil

Full text with 50 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055598/>

Δ -9-tetrahydrocannabinol (Δ -9-THC) and Cannabidiol (CBD), the two main ingredients of the Cannabis sativa plant have distinct symptomatic and behavioral effects. We used functional magnetic resonance imaging (fMRI) in healthy volunteers to examine whether Δ -9-THC and CBD had opposite effects on regional brain function. We then assessed whether pretreatment with CBD can prevent the acute psychotic symptoms induced by Δ -9-THC. Fifteen healthy men with minimal earlier exposure to cannabis were scanned while performing a verbal memory task, a response inhibition task, a sensory processing task, and when viewing fearful faces. Subjects were scanned on three occasions, each preceded by oral administration of Δ -9-THC, CBD, or placebo. BOLD responses were measured using fMRI. In a second experiment, six healthy volunteers were administered Δ -9-THC intravenously on two occasions, after placebo or CBD pretreatment to examine whether CBD could block the psychotic symptoms induced by Δ -9-THC. Δ -9-THC and CBD had opposite effects on activation relative to placebo in the striatum during verbal recall, in the hippocampus during the response inhibition task, in the amygdala when subjects viewed fearful faces, in the superior temporal cortex when subjects listened to speech, and in the occipital cortex during visual processing. In the second experiment, pretreatment with CBD prevented the acute induction of psychotic symptoms by Δ -9-tetrahydrocannabinol. Δ -9-THC and CBD can have opposite effects on regional brain function, which may underlie their different symptomatic and behavioral effects, and CBD's ability to block the psychotogenic effects of Δ -9-THC.

Use of Cannabis for Medicinal Purposes

Resolutions 910, I-08; 921, I-08; and 229, A-09
Reference Committee K
Executive Summary

Full text, PDF, with 101 references

http://www.procon.org/sourcefiles/AMAReport_CouncilSciencePublicHealth.pdf

Objective. This report: (1) provides a brief historical perspective on the use of cannabis as medicine; (2) examines the current federal and state-based legal envelope relevant to the medical use of cannabis; (3) provides a brief overview of our current understanding of the pharmacology and physiology of the endocannabinoid system; (4) reviews clinical trials on the relative safety and efficacy of smoked cannabis and botanical-based products; and (5) places this information in perspective with respect to the current drug regulatory framework.

Data Sources. English-language reports on studies using human subjects were selected from a PubMed search of the literature from 2000 to August 2009 using the MeSH terms “marijuana,” “cannabis,” and tetrahydrocannabinol,” or “cannabinoids,” in combination with “drug effects,” “therapeutic use,” “administration & dosage,” “smoking,” “metabolism,” “physiology,” “adverse effects,” and “pharmacology.” Additionally the terms “abuse/epidemiology,” and “receptors, cannabinoid” in combination with “agonists,” or “antagonists & inhibitors” as well as “endocannabinoids,” in combination with “pharmacology,” “physiology,” or “metabolism” were used. Additional articles were identified by manual review of the references cited in these publications. Web sites of the Food and Drug Administration, Drug Enforcement Administration, National Institute on Drug Abuse, Marijuana Policy Project, ProCon.org, and the International Association for Cannabis as Medicine also were searched for relevant resources.

Results. The cannabis sativa plant contains more than 60 unique structurally related chemicals (phytocannabinoids). Thirteen states have enacted laws to remove state-level criminal penalties for possessing marijuana for qualifying patients, however the federal government refuses to recognize that the cannabis plant has an accepted medical benefit. Despite the public controversy, less than 20 small randomized controlled trials of short duration involving ~300 patients have been conducted over the last 35 years on smoked cannabis. Many others have been conducted on FDA-approved oral preparations of THC and synthetic analogues, and more recently on botanical extracts of cannabis. Federal court cases have upheld the privileges of doctor-patient discussions on the use of cannabis for medicinal purposes but also preserved the right of the federal government to prosecute patients using cannabis for medicinal purposes. Efforts to reschedule marijuana from Schedule I of the Controlled Substances Act have been unsuccessful to date. Disagreements persist about the long term consequences of marijuana use for medicinal purposes.

Conclusions. Results of short term controlled trials indicate that smoked cannabis reduces neuropathic pain, improves appetite and caloric intake especially in patients with reduced muscle mass, and may relieve spasticity and pain in patients with multiple sclerosis. However, the patchwork of state-based systems that have been established for “medical marijuana” is woefully inadequate in establishing even rudimentary safeguards that normally

would be applied to the appropriate clinical use of psychoactive substances. The future of cannabinoid-based medicine lies in the rapidly evolving field of botanical drug substance development, as well as the design of molecules that target various aspects of the endocannabinoid system. To the extent that rescheduling marijuana out of Schedule I will benefit this effort, such a move can be supported.

AMA Policy On Medical Marijuana

(1) Our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease. (2) Our AMA recommends that marijuana be retained in Schedule I of the Controlled Substances Act pending the outcome of such studies. (3) Our AMA urges the National Institutes of Health (NIH) to implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research into the medical utility of marijuana. This effort should include: a) disseminating specific information for researchers on the development of safeguards for marijuana clinical research protocols and the development of a model informed consent on marijuana for institutional review board evaluation; b) sufficient funding to support such clinical research and access for qualified investigators to adequate supplies of marijuana for clinical research purposes; c) confirming that marijuana of various and consistent strengths and/or placebo will be supplied by the National Institute on Drug Abuse to investigators registered with the Drug Enforcement Agency who are conducting bona fide clinical research studies that receive Food and Drug Administration approval, regardless of whether or not the NIH is the primary source of grant support. (4) Our AMA believes that the NIH should use its resources and influence to support the development of a smoke-free inhaled delivery system for marijuana or delta-9-tetrahydrocannabinol (THC) to reduce the health hazards associated with the combustion and inhalation of marijuana. (5) Our AMA believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between physicians and patients should not subject either party to

Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival

Marcu JP¹, Christian RT, Lau D, Zielinski AJ, Horowitz MP, Lee J, Pakdel A, Allison J, Limbad C, Moore DH, Yount GL, Desprez PY, McAllister SD.

1. California Pacific Medical Center Research Institute, San Francisco, California 94107, USA

Full text with 41 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806496/>

The cannabinoid 1 (CB(1)) and cannabinoid 2 (CB(2)) receptor agonist Delta(9)-tetrahydrocannabinol (THC) has been shown to be a broad-range inhibitor of cancer in culture and in vivo, and is currently being used in a clinical trial for the treatment of glioblastoma. It has been suggested that other plant-derived cannabinoids, which do not interact efficiently with CB(1) and CB(2) receptors, can modulate the actions of Delta(9)-THC. There are conflicting reports, however, as to what extent other cannabinoids can modulate Delta(9)-THC activity, and most importantly, it is not clear whether other cannabinoid compounds can either potentiate or inhibit the actions of Delta(9)-THC. We therefore tested cannabidiol, the second most abundant plant-derived cannabinoid, in combination with Delta(9)-THC. In the U251 and SF126 glioblastoma cell lines, Delta(9)-THC and cannabidiol acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle and induction of reactive oxygen species and apoptosis as well as specific modulations of extracellular signal-regulated kinase and caspase activities. These specific changes were not observed with either compound individually, indicating that the signal transduction pathways affected by the combination treatment were unique. Our results suggest that the addition of cannabidiol to Delta(9)-THC may improve the overall effectiveness of Delta(9)-THC in the treatment of glioblastoma in cancer patients.

The endocannabinoid system during development: emphasis on perinatal events and delayed effects

Fride E1, Gobshtis N, Dahan H, Weller A, Giuffrida A, Ben-Shabat S.

Department of Behavioral Sciences and Molecular Biology, Ariel University Center of Samaria, Ariel, Israel

<http://www.ncbi.nlm.nih.gov/pubmed/19647111>

The endocannabinoid system (ECS) including its receptors, endogenous ligands (“endocannabinoids”), synthesizing and degrading enzymes, and transporter molecules has been detected from the earliest embryonal stages and throughout pre- and postnatal development; endocannabinoids, notably 2-arachidonoylglycerol, are also present in maternal milk. During three developmental stages, (1) early embryonal, (2) prenatal brain development, and (3) postnatal suckling, the ECS plays an essential role for development and survival. During early gestation, successful embryonal passage through the oviduct and implantation into the uterus require critical enzymatic control of the endocannabinoids. During fetal life, endocannabinoids and the cannabinoid CB(1) receptor are important for brain development, regulating neural progenitor differentiation and guiding axonal migration and synaptogenesis. Postnatally, CB(1) receptor activation by 2-arachidonoylglycerol appears to play a critical role in the initiation of milk suckling in mouse pups, possibly by enabling innervation and/or activation of the tongue muscles. Perinatal manipulation of the ECS, by administering cannabinoids or by maternal marijuana consumption, alters neurotransmitter and behavioral functions in the offspring. Interestingly, the sequelae of prenatal cannabinoids are similar to many effects of prenatal stress, which may suggest that prenatal stress impacts on the ECS and that vice versa prenatal cannabinoid exposure may interfere with the ability of the fetus to cope with the stress. Future studies should further clarify the mechanisms involved in the developmental roles of the ECS and understand better the adverse effects of prenatal exposure, to design strategies for the treatment of conditions including infertility, addiction, and failure-to-thrive.

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The endocannabinoid system and pain

Guindon J1, Hohmann AG.

Neuroscience and Behavior Program, Department of Psychology, University of Georgia, Athens, GA 30602-3013, USA

Full text with 259 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834283/>

The therapeutic potential of cannabinoids has been the topic of extensive investigation following the discovery of cannabinoid receptors and their endogenous ligands. Cannabinoid receptors and their endogenous ligands are present at supraspinal, spinal and peripheral levels. Cannabinoids suppress behavioral responses to noxious stimulation and suppress nociceptive processing through activation of cannabinoid CB(1) and CB(2) receptor subtypes. Endocannabinoids, the brain's own cannabis-like substances, share the same molecular target as Delta(9)-tetrahydrocannabinol, the main psychoactive component in cannabis. Endocannabinoids serve as synaptic circuit breakers and regulate multiple physiological and pathological conditions, e.g. regulation of food intake, immunomodulation, inflammation, analgesia, cancer, addictive behavior, epilepsy and others. This review will focus on uncovering the roles of anandamide and 2-arachidonoylglycerol, the two best characterized endocannabinoids identified to date, in controlling nociceptive responding. The roles of anandamide and 2-arachidonoylglycerol, released under physiological conditions, in modulating nociceptive responding at different levels of the neuraxis will be emphasized in this review. Effects of modulation of endocannabinoid levels through inhibition of endocannabinoid hydrolysis and uptake is also compared with effects of exogenous administration of synthetic endocannabinoids in acute, inflammatory and neuropathic pain models. Finally, the therapeutic potential of the endocannabinoid signaling system is discussed in the context of identifying novel pharmacotherapies for the treatment of pain.

Bogarting that joint might decrease oral HPV among cannabis users

By S.R. Zwenger

School of Biological Sciences, University of Northern Colorado, Ross Hall 2480, Box 92, 501–20 Street, Greeley, Colorado 80631 USA
sam.zwenger@gmail.com

Full text with 26 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2794675/>

Human papilloma virus (hpv) has many known strains, two of the most well studied perhaps being the high-risk types 16 and 18. These strains have attracted more interest because they are known to disrupt tumour-suppressor genes that control the cell cycle, rendering those genes less effective at keeping cell division in check.

Within the last decade, an increase in oral hpv–linked cancers of the throat and tongue has been attributed to exposure and contraction of hpv through oral sex, most notably in younger people. An understudied and arguably equal contributor to oral hpv infection might be indirect contact with an infected person. Presented here is a brief but important perspective on the relationship between cannabis use and oral cancer. The development of oral cancer is not a result of smoking cannabis per se; rather, it is hypothesized to be a result of contracting hpv through various forms of sharing and passing joints and other smoking apparatuses. Therefore, it is hypothesized that bogarting (and not passing) joints might decrease oral hpv among cannabis smokers. Future research should therefore investigate the prevalence of oral hpv in cannabis smokers to better understand its epidemiology.

1. INTRODUCTION

The American Cancer Society estimates that, in the United States, more than 6 million people contract human papilloma virus (hpv) each year and that nearly half are between 15 and 25 years of age. Oral sex with an hpv-infect-

ed person has been shown possibly to increase the likelihood of contracting oral hpv1. Expression of either E6 or E7 high-risk hpv (types 16 and 18) oncoprotein is known to interfere with the cell-cycle tumour suppressors p53 and pBR. Sustained expression of these oncoproteins is ultimately able to drive chromosomal mutations, which lead to cancerous cells2.

Patients treated for head-and-neck cancers can have a drastically degraded quality of life. For example, in many cases, treatment and surgeries can lead to increased depression, increased anxiety, and decreased marital quality, and can cause difficulty with daily tasks such as eating and speaking3. Chandu et al.4 assert that understanding the impact of oral cancer on patients can be better determined with the use of surveys that assess their health-related quality of life, and can also lead to better patient care. Previously, such surveys were used primarily in research settings.

The rapid rise in oral cancers among young people is expected to continue. This rise has largely been attributed to contraction of oral hpv through sexual behaviours (for example, oral sex). Additionally, Rose Ragin et al.5 showed that women with hpv-related cervical cancer had a higher chance of head-and-neck cancer. Using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results database, they found that women with cervical cancer had a greater chance of developing head-and-neck squamous cell carcinomas. The authors suggested that the head-and-neck cancers are caused by secondary infections from hpv. D'Souza et al.6 determined that

oropharyngeal cancer and infection with oral hpv are strongly linked. They also suggest that oral hpv is often contracted through oral sex. However, Sok and Grandis⁷ stated that some of the routes of oral hpv infection are unknown. Regardless, many people have suggested that a vaccine against oral hpv might be important in preventing oral hpv infections^{8–10}.

2. DISCUSSION

2.1 Oral HPV and Cannabis

Given these considerations, there has been much debate on whether cannabis has been a causative agent of oral cancers. As with hpv-linked cancers, studies have tried to find a relationship between cannabis smoking and a variety of types of cancers. For example, Almadori et al.¹¹ postulated a link between cannabis smoking and tongue carcinomas. Hashibe et al.¹² conducted a study on 2252 subjects, including people with and without cancer, and found no relationship between cannabis use and lung and aerodigestive tract cancers. Some authors have hypothesized that cannabis use might be a cause of transitional cell carcinoma, a type of bladder cancer typically associated with tobacco smokers^{13,14}. Hall et al.¹⁵ reviewed the relationships between cancer and cannabis, including its possible role as a cause of cancer and its use to relieve pain in cancer patients. Others have reviewed cannabis use and the probability of developing cancer¹⁶. In a more recent study, Aldington et al.¹⁷ investigated the relationship between cannabis and head-and-neck cancer and found little or no correlation.

However, in all of the above-mentioned studies and reviews, hpv as a possible factor in the development of cancer was not discussed. The importance of understanding the role that cannabis smoking might play in hpv-related cancers is difficult to overstate. Indeed, a recent report by the World Health Organization notes that countries must begin to take action toward dealing

with oral cancer prevention¹⁸. If cannabis use is indeed a major contributor to spreading oral hpv, steps should be taken by governments to educate their citizens to help mitigate oral cancer rates.

Worldwide consumption of cannabis has been documented by the United Nations World Drug Report¹⁹. Based on the report's estimates, 165,600,000 people used cannabis in 2006. North America and Europe accounted for about 70 million of those users, both regions being above the global average. A report by Leatherdale et al.²⁰ states that nearly half of Canadian adults 18 years of age or older have tried cannabis in spite of its illegality. However, some countries have recognized the medicinal properties of this plant product and approved it for medical use, which may also contribute to the observed increase in use. For example, part of the increased cannabis use in Canada is based on the fact that, although cannabis is classified as an illegal drug, individuals who are living with a qualifying debilitating illness can legally obtain it through Health Canada's Medical Marijuana Access Division. The possibility that hpv can be passed among cannabis users is therefore significant.

The human papilloma virus can be found on the surface of the lips, the lining of the mouth, on the tongue, and so on. Therefore, as an infected person places a cannabis cigarette or smoking device on their lips, they simultaneously deposit viral particles on the device. The hpv remains there until another user places the same area of the smoking device onto their lips. This scenario could easily have continued for many years as a possible method of oral hpv transmission.

Although partaking in cannabis smoking may be an individual process, cannabis smokers are also known to pass and share their cannabis freely. For instance, various studies have found that, although some cannabis users smoke alone, others share with close friends or at parties, making smok-

ing a social activity^{21,22}. Dunlap et al.²³ observed that sharing cannabis wrapped in a cigar shell (called a “blunt”) often occurs among large groups of people.

2.2 Needed Research

Gillison and Lowy²⁴ discussed some ways in which people might contract hpv and postulated reasons that vaccines might be useful in controlling hpv-related cancers in later life. They cited use of alcohol and tobacco (because of the carcinogenic nature of those substances) as additional contributors to the likelihood that these types of cancers may develop. The mention of tobacco is interesting, because it, too, may serve as an indirect route of transmission. For example, Knishkowsky and Amitai²⁵ discuss tobacco smoking through water pipes, a practice that is very common in most Middle Eastern countries. They warn of the rise of “hooka bars” and their negative impact on the health of young adults, because this group seems to be the main one using tobacco water pipes. Although they mention that sharing of these pipes can lead to a variety of diseases, hpv is not mentioned. Still, sharing tobacco-smoking devices could also serve as an additional route of oral hpv contraction. To compound matters further, it is not exactly known how easily oral hpv can be transmitted between individuals (for example, through sharing water bottles in sports or through casual kissing).

With such uncertainty, one would hope that a rapid assay for oral hpv would soon be available. Such a test might prove useful in a clinical setting, for research purposes, or for personal knowledge. Currently, in individuals positive for oral hpv, hpv antibodies can be detected in the mucosal areas.

Marais et al.²⁶ described a study in which they used an enzyme-linked immunosorbent assay to detect hpv antibodies from oral swabs. This same method might be desirable in a controlled study of cannabis users in future research. A study of this nature could provide a relatively rapid analysis of cannabis users and rates of hpv (for example, testing positive or negative as oral hpv carriers). Additionally, because cannabis use is often higher among men, higher rates of oral cancer might be observed in men than in women. Studying the frequency of cannabis use might also result in important findings such as an increased likelihood of users testing positive for oral hpv. Comparing individuals that share cannabis in group settings with those who consume cannabis alone might provide insight into more definitive patterns of oral hpv and thus help to predict the likelihood of head-and-neck cancers developing in later life.

3. CONCLUSIONS

It certainly may not be the cannabis smoke that causes oral cancers in heavy cannabis users. Most people who have ever smoked cannabis have most likely done so by sharing a rolled cigarette or pipe in a group setting. The sharing and passing of these smoking devices from an oral hpv-infected individual to an uninfected individual could easily provide a route of transmission for the virus between users. Frequency and setting should therefore be considered two major factors that might contribute to the likelihood of acquiring oral hpv. Thus, the relationship between cannabis and various cancer types might not be from cannabis use itself, but rather from contracting high-risk types of oral hpv that lead to cancer in later life.

Role of cannabis and endocannabinoids in the genesis of schizophrenia

Fernandez-Espejo E1, Viveros MP, Núñez L, Ellenbroek BA, Rodriguez de Fonseca F.

Departamento de Fisiología Médica, Facultad de Medicina, Universidad de Sevilla, Seville, Spain
efespejo@us.es

<http://www.ncbi.nlm.nih.gov/pubmed/19629449>

Cannabis abuse and endocannabinoids are associated to schizophrenia.

It is important to discern the association between schizophrenia and exogenous Cannabis sativa, on one hand, and the endogenous cannabinoid system, on the other hand.

On one hand, there is substantial evidence that cannabis abuse is a risk factor for psychosis in genetically predisposed people, may lead to a worse outcome of the disease, or it can affect normal brain development during adolescence, increasing the risk for schizophrenia in adulthood. Regarding genetic predisposition, alterations affecting the cannabinoid CNR1 gene could be related to schizophrenia. On the other hand, the endogenous cannabinoid system is altered in schizophrenia (i.e., increased density of cannabinoid CB1 receptor binding in corticolimbic regions, enhanced cerebrospinal fluid anandamide levels), and dysregulation of this system can interact with neurotransmitter systems in such a way that a “cannabinoid hypothesis” can be integrated in the neurobiological hypotheses of schizophrenia. Finally, there is also evidence that some genetic alterations of the CNR1 gene can act as a protectant factor against schizophrenia or can induce a better pharmacological response to atypical antipsychotics.

Cannabis abuse is a risk factor for psychosis in predisposed people, it can affect neurodevelopment during adolescence leading to schizophrenia, and a dysregulation of the endocannabinoid system can participate in schizophrenia. It is also worth noting that some specific cannabinoid alterations can act as neuroprotectant for schizophrenia or can be a psychopharmacogenetic rather than a vulnerability factor.

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Cannabinoids and atherosclerosis

By Z. Fisar

Charles University in Prague, First Faculty of Medicine, Department of Psychiatry, Prague, Czech Republic
zfsar@lf1.cuni.cz

<http://www.ncbi.nlm.nih.gov/pubmed/19591373>

The endocannabinoids are a family of lipid neurotransmitters that engage the same membrane receptors targeted by tetrahydrocannabinol and that mediate retrograde signal from postsynaptic neurons to presynaptic ones. Discovery of endogenous cannabinoids and studies of the physiological functions of the cannabinoid system in the brain and body are producing a number of important findings about the role of membrane lipids and fatty acids. The role of lipid membranes in the cannabinoid system follows from the fact that the source and supply of endogenous cannabinoids are derived from arachidonic acid. The study of molecules which influence the cannabinoid system in the brain and body is crucial in search of medical preparations with the therapeutic effects of the phytocannabinoids without the negative effects on cognitive function attributed to cannabis. Basic information about function and role of the endocannabinoid system is summarized in the paper; possible therapeutic action of cannabinoids, effects on atherosclerosis specially, is described at the close.

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Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis

Storr MA1, Keenan CM, Zhang H, Patel KD, Makriyannis A, Sharkey KA.

1. Division of Gastroenterology, Department of Medicine and Snyder Institute of Infection, Immunity & Inflammation, University Calgary, Calgary, Alberta, Canada
mstorr@ucalgary.ca

<http://www.ncbi.nlm.nih.gov/pubmed/19408320>

Activation of cannabinoid (CB)(1) receptors results in attenuation of experimental colitis. Our aim was to examine the role of CB(2) receptors in experimental colitis using agonists (JWH133, AM1241) and an antagonist (AM630) in trinitrobenzene sulfonic acid (TNBS)-induced colitis in wildtype and CB(2) receptor-deficient (CB(2) (-/-)) mice.

We show that activation of the CB(2) receptor protects against experimental colitis in mice. Increased expression of CB(2) receptor mRNA and aggravation of colitis by AM630 suggests a role for this receptor in normally limiting the development of colitis. These results support the idea that the CB(2) receptor may be a possible novel therapeutic target in inflammatory bowel disease.

The adverse health effects of cannabis use: what are they, and what are their implications for policy?

By W. Hall

School of Population Health, University of Queensland, Herston Road, Herston QLD, 4006, Australia
w.hall@sph.uq.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/19362460>

The adverse health effects of cannabis are a source of contention in debates about policies towards the drug. This paper provides a review of epidemiological evidence on the major adverse health effects of cannabis use and considers its implications for policy.

The evidence strongly suggests that cannabis can adversely affect some users, especially adolescents who initiate use early and young adults who become regular users. These adverse effects probably include increased risks of: motor vehicle crashes, the development of cannabis dependence, impaired respiratory function, cardiovascular disease, psychotic symptoms, and adverse outcomes of adolescent development, namely, poorer educational outcomes and an increased likelihood of using other illicit drugs.

Politically, evidence of adverse health effects favours the status quo in developed countries like Australia where cannabis policy has been framed by the media as a choice between two views: (1) either cannabis use is largely harmless to most users and so we should legalize, or at the very least decriminalize its use; or (2) it harms some of its users so we should continue to prohibit its use.

Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome

Jutras-Aswad D1, DiNieri JA, Harkany T, Hurd YL.

1. Department of Psychiatry, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029, USA

<http://www.ncbi.nlm.nih.gov/pubmed/19568685>

Despite the high prevalence of marijuana use among pregnant women and adolescents, the impact of cannabis on the developing brain is still not well understood. However, growing evidence supports that the endocannabinoid system plays a major role in CNS patterning in structures relevant for mood, cognition, and reward, such as the mesocorticolimbic system. It is thus clear that exposure to cannabis during early ontogeny is not benign and potential compensatory mechanisms that might be expected to occur during neurodevelopment appear insufficient to eliminate vulnerability to neuropsychiatric disorders in certain individuals. Both human longitudinal cohort studies and animal models strongly emphasize the long-term influence of prenatal cannabinoid exposure on behavior and mental health. This review provides an overview of the endocannabinoid system and examines the neurobiological consequences of cannabis exposure in pregnancy and early life by addressing its impact on the development of neurotransmitters systems relevant to neuropsychiatric disorders and its association with these disorders later in life. It posits that studying in utero cannabis exposure in association with genetic mutations of neural systems that have strong relationships to endocannabinoid function, such as the dopamine, opioid, glutamate, and GABA, might help to identify individuals at risk. Such data could add to existing knowledge to guide public health platform in regard to the use of cannabis and its derivatives during pregnancy.

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Adverse health effects of non-medical cannabis use

Hall W1, Degenhardt L.

School of Population Health, University of Queensland, Herston, QLD, Australia
w.hall@sph.uq.edu.au

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For over two decades, cannabis, commonly known as marijuana, has been the most widely used illicit drug by young people in high-income countries, and has recently become popular on a global scale. Epidemiological research during the past 10 years suggests that regular use of cannabis during adolescence and into adulthood can have adverse effects. Epidemiological, clinical, and laboratory studies have established an association between cannabis use and adverse outcomes. We focus on adverse health effects of greatest potential public health interest—that is, those that are most likely to occur and to affect a large number of cannabis users. The most probable adverse effects include a dependence syndrome, increased risk of motor vehicle crashes, impaired respiratory function, cardiovascular disease, and adverse effects of regular use on adolescent psychosocial development and mental health.

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Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb

Izzo AA1, Borrelli F, Capasso R, Di Marzo V, Mechoulam R.

Department of Experimental Pharmacology, University of Naples Federico II, Naples, Italy
aaizzo@unina.it

<http://www.ncbi.nlm.nih.gov/pubmed/19729208>

Delta(9)-tetrahydrocannabinol binds cannabinoid (CB(1) and CB(2)) receptors, which are activated by endogenous compounds (endocannabinoids) and are involved in a wide range of physiopathological processes (e.g. modulation of neurotransmitter release, regulation of pain perception, and of cardiovascular, gastrointestinal and liver functions). The well-known psychotropic effects of Delta(9)-tetrahydrocannabinol, which are mediated by activation of brain CB(1) receptors, have greatly limited its clinical use. However, the plant Cannabis contains many cannabinoids with weak or no psychoactivity that, therapeutically, might be more promising than Delta(9)-tetrahydrocannabinol. Here, we provide an overview of the recent pharmacological advances, novel mechanisms of action, and potential therapeutic applications of such non-psychotropic plant-derived cannabinoids. Special emphasis is given to cannabidiol, the possible applications of which have recently emerged in inflammation, diabetes, cancer, affective and neurodegenerative diseases, and to Delta(9)-tetrahydrocannabinol, a novel CB(1) antagonist which exerts potentially useful actions in the treatment of epilepsy and obesity.

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Cannabis use in pregnancy and early life and its consequences: animal models

By M. Schneider

Department of Psychopharmacology, Central Institute of Mental Health (ZI), J5, 68159 Mannheim, Germany
miriam.schneider@zi-mannheim.de

Abstract only with 69 hyper-linked references

<http://link.springer.com/article/10.1007%2Fs00406-009-0026-0>

Cannabinoid receptors and their endogenous ligands have been detected from the earliest stages of embryonic development. The endocannabinoid system appears to play essential roles in these early stages for neuronal development and cell survival, although its detailed involvement in fundamental developmental processes such as proliferation, migration and differentiation has not yet been completely understood. Therefore, it is not surprising that manipulations of the endocannabinoid system by cannabinoid exposure during early developmental stages can result in long-lasting neurobehavioural consequences. The present review will summarize the possible residual behavioural effects of cannabinoid administration during pre- and perinatal as well as early postnatal development, derived from animal studies.

The endocannabinoid system and the regulation of neural development: potential implications in psychiatric disorders

Galve-Roperh I1, Palazuelos J, Aguado T, Guzmán M.

Department of Biochemistry and Molecular Biology I, School of Biology and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Complutense University, 28040 Madrid, Spain
igr@quim.ucm.es

<http://www.ncbi.nlm.nih.gov/pubmed/19588184>

During brain development, functional neurogenesis is achieved by the concerted action of various steps that include the expansion of progenitor cells, neuronal specification, and establishment of appropriate synapses. Brain patterning and regionalization is regulated by a variety of extracellular signals and morphogens that, together with neuronal activity, orchestrate and regulate progenitor proliferation, differentiation, and neuronal maturation. In the adult brain, CB(1) cannabinoid receptors are expressed at very high levels in selective areas and are engaged by endocannabinoids, which act as retrograde messengers controlling neuronal function and preventing excessive synaptic activity. In addition, the endocannabinoid system is present at early developmental stages of nervous system formation. Recent studies have provided novel information on the role of this endogenous neuromodulatory system in the control of neuronal specification and maturation. Thus, cannabinoid receptors and locally produced endocannabinoids regulate neural progenitor proliferation and pyramidal specification of projecting neurons. CB(1) receptors also control axonal navigation, migration, and positioning of interneurons and excitatory neurons. Loss of function studies by genetic ablation or pharmacological blockade of CB(1) receptors interferes with long-range subcortical projections and, likewise, prenatal cannabinoid exposure induces different functional alterations in the adult brain. Potential implications of these new findings, such as the participation of the endocannabinoid system in the pathogenesis of neurodevelopmental disorders (e.g., schizophrenia) and the regulation of neurogenesis in brain depression, are discussed herein.

Cannabis and psychosis: search of a causal link through a critical and systematic review

Le Bec PY1, Fatséas M, Denis C, Lavie E, Auriacombe M.

1. Laboratoire de psychiatrie, EA4139, faculté de médecine Victor-Pachon, institut fédératif de recherche en santé publique, Inserm-IFR no 99, université Victor-Segalen Bordeaux-2, Bordeaux, France

<http://www.ncbi.nlm.nih.gov/pubmed/19748375>

Although cannabis use may be involved in the aetiology of acute psychosis, there has been considerable debate about the association observed between cannabis use and chronic psychosis. In particular, because of the frequent co-occurrence between schizophrenia and cannabis use, the question has been raised of a causal link between exposure to cannabis as a risk factor and the development of psychosis or psychotic symptoms.

The aim of this article was to examine the evidence that cannabis use causes chronic psychotic disorders by using established criteria of causality. These criteria were defined by: biologic plausibility, strength of the interaction between the risk factor and the disease, repeatability of the results, temporal sequence between the exposure to the risk factor and the beginning of the disease and existence of a dose-effect relationship.

Together, the seven studies were all prospective cohorts and represented 50,275 human subjects. There were three European studies (from Sweden, Holland and Germany), one from New Zealand and one from Australia. Only one study of the seven did not show a significant association between cannabis consumption and increase of the risk of developing a psychosis. However, this study had some bias, such as low level of cannabis use and the lack of evaluation of cannabis use after inclusion. For the six other studies, data show the existence of a significant association between cannabis use and psychotic disorders (with an increased risk between 1.2 and 2.8 in Zammit et al.'s study), particularly among vulnerable individuals (that is with a prepsychotic state at the time of inclusion). Therefore, all the studies that assessed a dose-effect relationship showed this link between cannabis use and the emergence of psychosis or psychotic symptoms. The fact that all causal criteria were present in the studies suggests that cannabis use may be an independent risk factor for the development of psychosis. Results seem to be more consistent for vulnerable individuals with the hypothesis that cannabis use may precipitate psychosis, notably among vulnerable subjects. In particular, early onset of cannabis use during adolescence should be an environmental stressor that interacts with a genetic predisposition to induce a psychotic disorder.

The objective of this article was to examine whether cannabis use can be an independent risk factor for chronic psychotic disorders, by using established criteria of causality. Data extracted from the selected studies showed that cannabis use may be an independent risk factor for the development of psychotic disorders. Early screening of the vulnerability to psychotic disorder should permit improved focus on prevention and information about the specific risks related to cannabis use among this population.

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Cannabinoids and the skeleton: from marijuana to reversal of bone loss

Bab I1, Zimmer A, Melamed E.

Bone Laboratory, the Hebrew University of Jerusalem, Jerusalem, Israel
babi@cc.huji.ac.il

<http://www.ncbi.nlm.nih.gov/pubmed/19634029>

The active component of marijuana, Delta(9)-tetrahydrocannabinol, activates the CB1 and CB2 cannabinoid receptors, thus mimicking the action of endogenous cannabinoids. CB1 is predominantly neuronal and mediates the cannabinoid psychotropic effects. CB2 is predominantly expressed in peripheral tissues, mainly in pathological conditions. So far the main endocannabinoids, anandamide and 2-arachidonoylglycerol, have been found in bone at 'brain' levels. The CB1 receptor is present mainly in skeletal sympathetic nerve terminals, thus regulating the adrenergic tonic restraint of bone formation. CB2 is expressed in osteoblasts and osteoclasts, stimulates bone formation, and inhibits bone resorption. Because low bone mass is the only spontaneous phenotype so far reported in CB2 mutant mice, it appears that the main physiologic involvement of CB2 is associated with maintaining bone remodeling at balance, thus protecting the skeleton against age-related bone loss. Indeed, in humans, polymorphisms in CNR2, the gene encoding CB2, are strongly associated with postmenopausal osteoporosis. Preclinical studies have shown that a synthetic CB2-specific agonist rescues ovariectomy-induced bone loss. Taken together, the reports on cannabinoid receptors in mice and humans pave the way for the development of 1) diagnostic measures to identify osteoporosis-susceptible polymorphisms in CNR2, and 2) cannabinoid drugs to combat osteoporosis.

Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study)

Baeza I1, Graell M, Moreno D, Castro-Fornieles J, Parellada M, González-Pinto A, Payá B, Soutullo C, de la Serna E, Arango C.

1. Department of Child and Adolescent Psychiatry and Psychology, Institut Clinic of Neurosciences, Hospital Clínic Universitari, IDIBAPS, Barcelona, Spain
ibaeza@clinic.ub.es

<http://www.ncbi.nlm.nih.gov/pubmed/19427172?dopt=Abstract>

OBJECTIVE: To know the prevalence of substance use and its relationship with psychopathology at onset and after six months in children and adolescents with first episode psychosis (FEP).

110 FEP patients, aged 9-17, were assessed for substance use, and with the Positive and Negative Syndrome Scale (PANSS) and other psychopathological and general functioning scales at baseline and after a six-month follow-up.

Patients' substance use at baseline was: tobacco (30.9%), cannabis (29.1%), alcohol (21.8%), cocaine (8.2%), amphetamines (2.7%), LSD (1.8%) and opiates (0.90%). Six months later, there was a decrease in patients' use of cannabis ($p=0.004$) and other drugs, except tobacco. Patients were divided, according to their baseline cannabis use, into 32 cannabis users (CU) and 78 non-cannabis users (NCU). CU were older ($p=0.002$) and had higher PANSS positive scores ($p=0.002$) and lower PANSS negative ($p<0.001$), PANSS general ($p=0.002$) and PANSS total ($p=0.007$) scores than NCU. At six months, CU had significantly lower PANSS positive ($p=0.010$), negative ($p=0.0001$), general ($p=0.002$) and total ($p=0.002$) scores than NCU. When we divided CU at six months into previous CU ($n=16$) and current CU ($n=15$), previous CU had the best outcome, NCU the worst and current CU had an intermediate profile.

Cannabis use may be related to higher positive symptom scores for FEP patients, with greater improvement after six months for those who cease using cannabis.

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**The endocannabinoid system:
its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation**

By V. Di Marzo

Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, Comprensorio Olivetti, 80078 Pozzuoli, Naples, Italy
vdimarzo@icmib.na.cnr.it

<http://www.ncbi.nlm.nih.gov/pubmed/19559360>

The endocannabinoid signalling system includes: (1) at least two G-protein-coupled receptors, known as the cannabinoid CB(1) and CB(2) receptors and discovered following studies on the mechanism of action of Delta(9)-tetrahydrocannabinol, the major psychoactive principle of the hemp plant *Cannabis sativa*; (2) the endogenous agonists at these receptors, known as endocannabinoids, of which anandamide and 2-arachidonoylglycerol are the best known; and (3) proteins and enzymes for the regulation of endocannabinoid levels and action at receptors. The endocannabinoid system is quite widespread in mammalian tissues and cells and appears to play a pro-homeostatic role by being activated following transient or chronic perturbation of homeostasis, and by regulating in a local way the levels and action of other chemical signals. Compounds that selectively manipulate the action and levels of endocannabinoids at their targets have been and are being developed, and represent templates for potential new therapeutic drugs.

Hippocampal CB(1) receptors mediate the memory impairing effects of Delta(9)-tetrahydrocannabinol

Wise LE1, Thorpe AJ, Lichtman AH.

1. Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA

Full text with 55 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822461/>

It is firmly established that the hippocampus, a brain region implicated in spatial learning, episodic memory, and consolidation, contains a high concentration of CB(1) receptors. Moreover, systemic and intrahippocampal administration of cannabinoid agonists have been shown to impair hippocampal-dependent memory tasks. However, the degree to which CB(1) receptors in the hippocampus play a specific functional role in the memory disruptive effects of marijuana or its primary psychoactive constituent Delta(9)-tetrahydrocannabinol (Delta(9)-THC) is unknown. This study was designed to determine whether hippocampal CB(1) receptors play a functional role in the memory disruptive effects of systemically administered cannabinoids, using the radial arm maze, a well characterized rodent model of working memory. Male Sprague-Dawley rats were implanted with bilateral cannulae aimed at the CA1 region of the dorsal hippocampus. The CB(1) receptor antagonist, rimonabant, was delivered into the hippocampus before to a systemic injection of either Delta(9)-THC or the potent cannabinoid analog, CP-55,940. Strikingly, intrahippocampal administration of rimonabant completely attenuated the memory disruptive effects of both cannabinoids in the radial arm maze task, but did not affect other pharmacological properties of cannabinoids, as assessed in the tetrad assay (that is, hypomotility, analgesia, catalepsy, and hypothermia). Infusions of rimonabant just dorsal or ventral to the hippocampus did not prevent Delta(9)-THC-induced memory impairment, indicating that its effects on mnemonic function were regionally selective. These findings provide compelling evidence in support of the view that hippocampal CB(1) receptors play a necessary role in the memory disruptive effects of marijuana.

The endocannabinoid system as a target for novel anxiolytic and antidepressant drugs

Gaetani S1, DiPasquale P, Romano A, Righetti L, Cassano T, Piomelli D, Cuomo V.

Department of Physiology and Pharmacology, Sapienza University of Rome, P.le Aldo Moro 5, 00185 Rome, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/19607961>

Observational studies in humans suggest that exposure to marijuana and other cannabis-derived drugs produces a wide range of subjective effects on mood tone and emotionality. These observations have their counterpart in animal studies, showing that cannabinoid agonists strongly affect emotional reactivity in directions that vary depending on dose and context. Based on these evidence, the activation of central CB(1) receptor has emerged as potential target for the development of anti-anxiety and antidepressant therapies. However, the variable effects of exogenous cannabinoid agonists have gradually shifted the interest to the alternative approach of amplifying the effects of endogenous cannabinoids (EC), namely anandamide (AEA) and 2-arachidonoylglycerol (2-AG), by preventing their deactivation. The enzyme fatty acid amide hydrolase (FAAH) has been the target of intense research efforts aimed at developing potent and selective inhibitors that might prolong AEA actions in vivo. Among the inhibitors developed, the compound URB597 was found to potently inhibit FAAH activity in vivo and cause brain AEA levels to increase. Interestingly, the enhanced AEA tone produced by URB597 does not result in the behavioral effects typical of a direct-acting cannabinoid agonist. Though URB597 does not elicit a full-fledged cannabinoid profile of behavioral responses, it does elicit marked anxiolytic-like and antidepressant-like effects in rats and mice. Such effects involve the downstream activation of CB(1) receptors, since they are attenuated by the CB(1) antagonist SR141716 (rimonabant). Parallel to FAAH inhibition, similar results can also be observed by pharmacologically blocking the AEA transport system, which is responsible of the intracellular uptake of AEA from the synaptic cleft. The reason why FAAH inhibition approach produces a smaller set of cannabinomimetic effects might depend on the mechanism of EC synthesis and release upon neuronal activation and on the target selectivity of the drug. The mechanism of EC release is commonly referred to as "on request", since they are not synthesized and stored in synaptic vesicles, such as classical neurotransmitters, but are synthesized from membrane precursors and immediately released in the synaptic cleft following neuronal activation. The neural stimulation in specific brain areas, for example, those involved in the regulation of mood tone and/or emotional reactivity, would result in an increased EC tone in these same areas, but not necessarily in others. Therefore, inhibition of AEA metabolism activity could amplify CB(1) activation mainly where AEA release is higher. Furthermore, the inhibition of FAAH causes an accumulation of AEA but not 2-AG, which, being 200-fold more abundant than AEA in the brain, might differently modulate CB(1)-mediated behavioral responses. The evidence outlined above supports the hypothesis that the EC system plays an important role in anxiety and mood disorders and suggests that modulation of FAAH activity might be a pharmacological target for novel anxiolytic and antidepressant therapies.

Pain Physician • May 2009

Ethics, law, and pain management as a patient right

Hall JK1, Boswell MV.

Department of Anesthesiology, Texas Tech Health Sciences Center, Lubbock, TX 79424, USA

Full text, PDF, with 30 references

<http://www.painphysicianjournal.com/current/pdf?article=MTlxNQ%3D%3D&journal=49>

Ethical and legal considerations in pain management typically relate to 2 issues. The first refers to pain management as a human right. The second involves the nature of the patient-physician relationship as it relates to pain management. Although pain physicians often like to think of pain management as a human right, it remains difficult to support this position as a point of law or as a matter of ethics. Medical organizations generally do not define pain management as a specific duty of the physician, apart from the provision of competent medical care. To date, neither law nor ethics creates a duty of care outside of the traditional patient-physician relationship. Absent a universal duty, no universal right exists. Pursuing pain management as a fundamental human right, although laudable, may place the power of the government in the middle of the patient-physician relationship. Despite apparent altruistic motives, attempts to define pain management as a basic human right could have unintended consequences, such as nationalization of medicine to ensure provision of pain management for all patients.

Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC)

Hunault CC1, Mensinga TT, Böcker KB, Schipper CM, Kruidenier M, Leenders ME, de Vries I, Meulenbelt J.

1. National Poisons Information Center, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
claudine.hunault@rivm.nl

<http://www.ncbi.nlm.nih.gov/pubmed/19099294>

Delta(9)-Tetrahydrocannabinol (THC) is the main active constituent of cannabis. In recent years, the average THC content of some cannabis cigarettes has increased up to approximately 60 mg per cigarette (20% THC cigarettes). Acute cognitive and psychomotor effects of THC among recreational users after smoking cannabis cigarettes containing such high doses are unknown.

The objective of this study was to study the dose-effect relationship between the THC dose contained in cannabis cigarettes and cognitive and psychomotor effects for THC doses up to 69.4 mg (23%). This double-blind, placebo-controlled, randomised, four-way cross-over study included 24 non-daily male cannabis users (two to nine cannabis cigarettes per month). Participants smoked four cannabis cigarettes containing 0, 29.3, 49.1 and 69.4 mg THC on four exposure days. The THC dose in smoked cannabis was linearly associated with a slower response time in all tasks (simple reaction time, visuo-spatial selective attention, sustained attention, divided attention and short-term memory tasks) and motor control impairment in the motor control task. The number of errors increased significantly with increasing doses in the short-term memory and the sustained attention tasks. Some participants showed no impairment in motor control even at THC serum concentrations higher than 40 ng/mL. High feeling and drowsiness differed significantly between treatments.

Response time slowed down and motor control worsened, both linearly, with increasing THC doses. Consequently, cannabis with high THC concentrations may be a concern for public health and safety if cannabis smokers are unable to titrate to a high feeling corresponding to a desired plasma THC level.

The cannabinoid system and pain: towards new drugs?

By M. Beltramo

Institut de Recherche Schering-Plough, Parc Scientifique Biomédical San Raffaele, via Olgettina 58, 20132 Milan, Italie
massimiliano.beltramo@spcorp.com

<http://www.ncbi.nlm.nih.gov/pubmed/19358815>

The various components of the endocannabinoid system were discovered in the last twenty years. The cannabinoid system has attracted pharmacologists interest for its potential as therapeutic targets for several diseases ranging from obesity to Parkinson's disease and from multiple sclerosis to pain.

Research initially focused on cannabinoid receptor 1 (CB1), but, due to psychotropic side effects related to its activation, the attempts to develop an agonist drug for this receptor has been so far unsuccessful. Recently the possibility to target CB2 has emerged as an alternative for the treatment of pain. The main advantage of targeting CB2 resides in the possibility to elicit the analgesic effect without the psychotropic side effects. Evidence of the analgesic effect of CB2 selective agonists has been obtained in various models of both inflammatory and neuropathic chronic pain. To explain the mechanism at the basis of this analgesic effect different hypotheses have been proposed: effect on inflammatory cells, reduction of basal NGF tone, induction of beta-endorphin release from keratinocytes, direct action on nociceptors. Evidence in support of this last hypothesis comes from down regulation of capsaicin-induced CGRP release in spinal cord slices and Dorsal Root Ganglia (DRG) neurons in culture after treatment with CB2 selective agonists. CB2 agonists are probably acting through several mechanisms and thus CB2 represents an interesting and promising target in the chronic pain field. Further clarification of the mechanisms at the basis of CB2 analgesic effect would surely be an intriguing and stimulating area of research for the years to come.

Current Topics In Behavioral Neuroscience • March 2009

Roles of the endocannabinoid system in learning and memory

Marsicano G1, Lafenêtre P.

1. Group Molecular Mechanisms of Behavioural Adaptation

Research Centre INSERM U862 NeuroCentre Magendie Université Bordeaux 2, 146, rue Léo Saignat, Bordeaux, France

marsicano@bordeaux.inserm.fr

<http://www.ncbi.nlm.nih.gov/pubmed/21104385>

The endocannabinoid system (ECS) plays a central role in the regulation of learning and memory processes. The fine-tuned regulation of neural transmission by the system is likely to be the mechanism underlying this important function. In this chapter, we review the data in the literature showing the direct involvement of the physiological activation of cannabinoid receptors in the modulation of different forms of learning and memory. When possible, we also address the likely mechanisms of this involvement. Finally, given the apparent special role of the ECS in the extinction of fear, we propose a reasonable model to assess how neuronal networks could be influenced by the endocannabinoids in these processes. Overall, the data reviewed indicate that, despite the enormous progress of recent years, much is still to be done to fully elucidate the mechanisms of the ECS influence on learning and memory processes.

Trends In Pharmacological Science • February 2009

Role of ionotropic cannabinoid receptors in peripheral antinociception and antihyperalgesia

Akopian AN1, Ruparel NB, Jeske NA, Patwardhan A, Hargreaves KM.

1. Department of Endodontics, University of Texas Health Science Center at San Antonio, TX 78229, USA
akopian@UTHSCSA.edu

Full text with 65 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2863326/>

Despite the wealth of information on cannabinoid-induced peripheral antihyperalgesic and antinociceptive effects in many pain models, the molecular mechanism(s) for these actions remains unknown. Although metabotropic cannabinoid receptors have important roles in many pharmacological actions of cannabinoids, recent studies have led to the recognition of a family of at least five ionotropic cannabinoid receptors (ICRs). The known ICRs are members of the family of transient receptor potential (TRP) channels and include TRPV1, TRPV2, TRPV4, TRPM8 and TRPA1. Cannabinoid activation of ICRs can result in desensitization of the TRPA1 and TRPV1 channel activities, inhibition of nociceptors and antihyperalgesia and antinociception in certain pain models. Thus, cannabinoids activate both metabotropic and ionotropic mechanisms to produce peripheral analgesic effects. Here, we provide an overview of the pharmacology of TRP channels as ICRs.

International Reviews In Neurobiology • January 2009

Developmental exposure to cannabinoids causes subtle and enduring neurofunctional alterations

Campolongo P1, Trezza V, Palmery M, Trabace L, Cuomo V.

1. Department of Physiology and Pharmacology Vittorio Erspamer, Sapienza University of Rome, P.le A. Moro 5, 00185 Rome, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/19607965>

Cannabis sativa preparations are among the illicit drugs most commonly used by pregnant women in Western countries. Although they are often considered relatively harmless, increasing evidence suggests that developmental exposure to cannabinoids induces subtle neurofunctional alterations in the offspring. In the present review, we summarize human and animal evidence examining the behavioral and neurobiological effects of exposure to cannabinoids during pregnancy and lactation. These studies show that the endocannabinoid system plays a crucial role in the ontogeny of the central nervous system and its activation, during brain development, can induce subtle and long-lasting neurofunctional alterations.

International Journal Of Dental Hygiene • November 2008

Effect of cannabis usage on the oral environment: a review

Versteeg PA1, Slot DE, van der Velden U, van der Weijden GA.

1. Department of Periodontology, Academic Centre of Dentistry Amsterdam, Louwesweg 1, Amsterdam, The Netherlands
p.versteeg@acta.nl

<http://www.ncbi.nlm.nih.gov/pubmed/19138182>

Based on the limited data, it seems justified to conclude that with increasing prevalence of cannabis use, oral health care providers should be aware of cannabis-associated oral side effects, such as xerostomia, leukoedema and an increased prevalence and density of *Candida albicans*.

Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects

Ellgren M1, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, Devi LA, Hurd YL.

1. Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Full text with 61 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2745315/>

Adolescence is a critical phase of active brain development often characterized by the initiation of marijuana (*Cannabis sativa*) use. Limited information is known regarding the endogenous cannabinoid system of the adolescent brain as well as related neurotransmitters that appear sensitive to cannabis exposure. We recently observed that adult rats pre-exposed to Delta-9-tetrahydrocannabinol (THC) during adolescence self-administered higher amounts of heroin and had selective impairments of the enkephalin opioid system within the nucleus accumbens (NAc) implicated in reward-related behavior. To explore the ontogeny of the cannabinoid and opioid neuronal systems in association with adolescence THC exposure, rats were examined at different adolescent stages during an intermittent THC paradigm (1.5 mg/kg i.p. every third day) from postnatal days (PNDs) 28-49. Rat brains were examined 24 h after injection at PND 29 (early adolescence), PND 38 (mid adolescence) and PND 50 (late adolescence) and analyzed for endocannabinoids (anandamide and 2-arachidonoylglycerol), Met-enkephalin, cannabinoid CB(1) receptors and micro opioid receptors (microOR) in the NAc, caudate-putamen and prefrontal cortex (PFC). Of the markers studied, the endocannabinoid levels had the most robust alterations throughout adolescence and were specific to the PFC and NAc. Normal correlations between anandamide and 2-arachidonoylglycerol concentrations in the NAc (positive) and PFC (negative) were reversed by THC. Other significant THC-induced effects were confined to the NAc - increased anandamide, decreased Met-enkephalin and decreased microORs. These findings emphasize the dynamic nature of the mesocorticolimbic endocannabinoid system during adolescence and the selective mesocorticolimbic disturbance as a consequence of adolescent cannabis exposure.

A cannabinoid analogue of Delta9-tetrahydrocannabinol disrupts neural development in chick

Psychoyos D1, Hungund B, Cooper T, Finnell RH.

Center for Environmental and Genetic Medicine, Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, Texas 77030, USA
dpsychoyos@ibt.tamhsc.edu

<http://www.ncbi.nlm.nih.gov/pubmed/19040278>

Marijuana is the most commonly abused illicit drug by pregnant women. Its major psychoactive constituent, Delta(9)-THC (Delta(9)-tetrahydrocannabinol), crosses the placenta and accumulates in the foetus, potentially harming its development. In humans, marijuana use in early pregnancy is associated with miscarriage, a fetal alcohol-like syndrome, as well as learning disabilities, memory impairment, and ADHD in the offspring. Classical studies in the 1970 s have reached disparate conclusions as to the teratogenic effects of cannabinoids in animal models. Further, there is very little known about the immediate effects of Delta(9)-THC on early embryogenesis. We have used the chick embryo as a model in order to characterize the effects of a water-soluble Delta(9)-THC analogue, O-2545, on early development. Embryos were exposed to the drug (0.035 to 0.35 mg/ml) at gastrulation and assessed for morphological defects at stages equivalent to 9-14 somites. We report that O-2545 impairs the formation of brain, heart, somite, and spinal cord primordia. Shorter incubation times following exposure to the drug show that O-2545 interferes with the initial steps of head process and neural plate formation. Our results indicate that the administration of the cannabinoid O-2545 during early embryogenesis results in embryotoxic effects and serves to illuminate the risks of marijuana exposure during the second week of pregnancy, a time point at which most women are unaware of their pregnancies.

Nature Medicine • September 2008

Endocannabinoid signaling as a synaptic circuit breaker in neurological disease

Katona I1, Freund TF.

Institute of Experimental Medicine, Hungarian Academy of Sciences, Szigony utca 43, H-1083 Budapest, Hungary
katona@koki.hu

<http://www.ncbi.nlm.nih.gov/pubmed/18776886>

Cannabis sativa is one of the oldest herbal plants in the history of medicine. It was used in various therapeutic applications from pain to epilepsy, but its psychotropic effect has reduced its usage in recent medical practice. However, renewed interest has been fueled by major discoveries revealing that cannabis-derived compounds act through a signaling pathway in the human body. Here we review recent advances showing that endocannabinoid signaling is a key regulator of synaptic communication throughout the central nervous system. Its underlying molecular architecture is highly conserved in synapses from the spinal cord to the neocortex, and as a negative feed-back signal, it provides protection against excess presynaptic activity. The endocannabinoid signaling machinery operates on demand in a synapse-specific manner; therefore, its modulation offers new therapeutic opportunities for the selective control of deleterious neuronal activity in several neurological disorders.

Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action

By A.W. Zuardi

Department of Neurology, Psychiatry and Medical Psychology, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
awzuardi@fmrp.usp.br

Full text, PDF, with 121 references

<http://www.scielo.br/pdf/rbp/v30n3/a15v30n3.pdf>

The aim of this review is to describe the historical development of research on cannabidiol.

After the elucidation of the chemical structure of cannabidiol in 1963, the initial studies showed that cannabidiol was unable to mimic the effects of Cannabis. In the 1970's the number of publications on cannabidiol reached a first peak, having the research focused mainly on the interaction with delta9-THC and its antiepileptic and sedative effects. The following two decades showed lower degree of interest, and the potential therapeutic properties of cannabidiol investigated were mainly the anxiolytic, antipsychotic and on motor diseases effects. The last five years have shown a remarkable increase in publications on cannabidiol mainly stimulated by the discovery of its anti-inflammatory, anti-oxidative and neuroprotective effects. These studies have suggested a wide range of possible therapeutic effects of cannabidiol on several conditions, including Parkinson's disease, Alzheimer's disease, cerebral ischemia, diabetes, rheumatoid arthritis, other inflammatory diseases, nausea and cancer.

In the last 45 years it has been possible to demonstrate that CBD has a wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials.

Addiction • August 2008

Adolescent cannabis users at 24 years: trajectories to regular weekly use and dependence in young adulthood

Swift W1, Coffey C, Carlin JB, Degenhardt L, Patton GC.

National Drug and Alcohol Research Centre, University of New South Wales, Australia
w.swift@unsw.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/18855826>

Participants reported frequency of cannabis use for the past 6 months at each time-point in adolescence (age 14-17 years). Cannabis exposure was defined as: maximum frequency of use (occasional, weekly, daily), number of waves of use (1 or 2; 3-6) and first wave of use (early use: first waves 1-3). Young adult (24 years) outcomes were: weekly+ cannabis use and DSM-IV cannabis dependence, referred to collectively as problematic use.

Of those interviewed at age 24 (wave 8), 34% had reported cannabis use in adolescence (waves 1-6), 12% at a level of weekly or more frequent use; 37% of these adolescent cannabis users were using at least weekly at wave 8, with 20% exhibiting dependence. Persistent adolescent cannabis and tobacco use as well as persistent mental health problems were associated strongly with problematic cannabis use at 24 years, after adjustment for potential confounding factors.

Heavy, persistent and early-onset cannabis use were all strongly predictive of later cannabis problems. Even so, occasional use was not free of later problems. Where there was co-occurring tobacco use or persistent mental health problems, risks for later problem cannabis use was higher.

Antibacterial cannabinoids from *Cannabis sativa*: a structure-activity study

Appendino G1, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M, Smith E, Rahman MM.

1. Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università del Piemonte Orientale, 28100 Novara, Italy
appendino@pharm.unipmn.it

<http://www.ncbi.nlm.nih.gov/pubmed/18681481>

Marijuana (*Cannabis sativa*) has long been known to contain antibacterial cannabinoids, whose potential to address antibiotic resistance has not yet been investigated. All five major cannabinoids (cannabidiol (1b), cannabichromene (2), cannabigerol (3b), Delta (9)-tetrahydrocannabinol (4b), and cannabinol (5)) showed potent activity against a variety of methicillin-resistant *Staphylococcus aureus* (MRSA) strains of current clinical relevance. Activity was remarkably tolerant to the nature of the prenyl moiety, to its relative position compared to the n-pentyl moiety (abnormal cannabinoids), and to carboxylation of the resorcinyl moiety (pre-cannabinoids). Conversely, methylation and acetylation of the phenolic hydroxyls, esterification of the carboxylic group of pre-cannabinoids, and introduction of a second prenyl moiety were all detrimental for antibacterial activity. Taken together, these observations suggest that the prenyl moiety of cannabinoids serves mainly as a modulator of lipid affinity for the olivetol core, a per se poorly active antibacterial pharmacophore, while their high potency definitely suggests a specific, but yet elusive, mechanism of activity.

Neuroimage • July 2008

**Corpus callosum damage in heavy marijuana use:
preliminary evidence from diffusion tensor tractography and tract-based spatial statistics**

Arnone D1, Barrick TR, Chengappa S, Mackay CE, Clark CA, Abou-Saleh MT.

Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK
danilo.arnone@manchester.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/18424082>

Heavy marijuana use has well established long term consequences for cognition and mental health, but the effect on brain structure is less well understood. We used an MRI technique that is sensitive to the structural integrity of brain tissue combined with a white matter mapping tractography technique to investigate structural changes in the corpus callosum (CC). Diffusion tensor imaging (DTI) was obtained in eleven heavy marijuana users who started using marijuana in early adolescence and eleven age matched controls. Mean diffusivity (MD) and fractional anisotropy (FA) (which measure structural integrity and tract coherence, respectively) were analysed within the corpus callosum which was spatially defined using tractography and tract-based spatial statistics (TBSS). MD was significantly increased in marijuana users relative to controls in the region of the CC where white matter passes between the prefrontal lobes. This observation suggests impaired structural integrity affecting the fibre tracts of the CC and is in keeping with previous reports of altered and diversified activation patterns in marijuana users. There was a trend towards a positive correlation between MD and length of use suggesting the possibility of a cumulative effect of marijuana over time and that a younger age at onset of use may predispose individuals to structural white matter damage. Structural abnormalities revealed in the CC may underlie cognitive and behavioural consequences of long term heavy marijuana use.

Journal Of Cardiovascular Medicine • June 2008

Cannabis: a trigger for acute myocardial infarction? A case report

Cappelli F1, Lazzeri C, Gensini GF, Valente S.

Heart and Vessel Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
cappellifrancesco@inwind.it

<http://www.ncbi.nlm.nih.gov/pubmed/18545075>

Cannabis smoking is consistently increasing in Europe and after alcohol it is the most common recreational drug in the western world. Users and lay people believe that marijuana or hashish is safe. Over the past four decades, however, it has been well established that cannabis has pathophysiological effects on the cardiovascular system. Information concerning the link between cannabis consumption and myocardial infarction is limited and existing data are controversial on this topic. In our case report, we describe a case of a young man who after smoking marijuana experienced ST elevation myocardial infarction caused by acute thrombosis of the descending artery, submitted to efficacious primary coronary angioplasty.

The pharmacology of the endocannabinoid system: functional and structural interactions with other neurotransmitter systems and their repercussions in behavioral addiction

López-Moreno JA1, González-Cuevas G, Moreno G, Navarro M.

1. Department of Psychobiology, Faculty of Psychology, Campus de Somosaguas, Complutense University of Madrid, Spain
jalopezm@psi.ucm.es

<http://www.ncbi.nlm.nih.gov/pubmed/18422831>

Addiction is a chronic, recurring and complex disorder. It is characterized by anomalous behaviors that are linked to permanent or long-lasting neurobiological alterations. Furthermore, the endocannabinoid system has a crucial role in mediating neurotransmitter release as one of the main neuromodulators of the mammalian central nervous system. The purpose of the present review is to instruct readers about the functional and structural interactions between the endocannabinoid system and the main neurotransmitter systems of the central nervous system in the context of drug addiction. With this aim, we have systematically reviewed the main findings of most of the existing literature that explores cross-talk in the five brain areas that are most traditionally implicated in addiction: amygdala, prefrontal cortex, nucleus accumbens, hippocampus and ventral tegmental area (VTA). The neurotransmission systems influenced by the pharmacology of the endocannabinoid system in these brain areas, which are reviewed here, are gamma-aminobutyric acid (GABA), glutamate, the main biogenic amines (dopamine, noradrenaline and serotonin), acetylcholine and opioids. We show that all of these neurotransmitter systems can be modulated differentially in each brain area by the activation or deactivation of cannabinoid CB1 brain receptors. Specifically, most of the studies relate to the hippocampus and nucleus accumbens. Moreover, the neurotransmitter with the fewest number of related studies is acetylcholine (excepting in the hippocampus), whereas there is a large number that evaluates GABA, glutamate and dopamine. Finally, we propose a possible interpretation of the role of the endocannabinoid system in the phenomenon of addiction.

Addiction Biology • June 2008

The endocannabinoid system: emotion, learning and addiction

Moreira FA1, Lutz B.

Department of Physiological Chemistry, Johannes Gutenberg University Mainz, Duesbergweg 6, 55099 Mainz, Germany
moreira@uni-mainz.de

<http://www.ncbi.nlm.nih.gov/pubmed/18422832>

The identification of the cannabinoid receptor type 1 (CB1 receptor) was the milestone discovery in the elucidation of the behavioural and emotional responses induced by the Cannabis sativa constituent Delta(9)-tetrahydrocannabinol. The subsequent years have established the existence of the endocannabinoid system. The early view relating this system to emotional responses is reflected by the fact that N-arachidonoyl ethanolamine, the pioneer endocannabinoid, was named anandamide after the Sanskrit word 'ananda', meaning 'bliss'. However, the emotional responses to cannabinoids are not always pleasant and delightful. Rather, anxiety and panic may also occur after activation of CB1 receptors. The present review discusses three properties of the endocannabinoid system as an attempt to understand these diverse effects. First, this system typically functions 'on-demand', depending on environmental stimuli and on the emotional state of the organism. Second, it has a wide neuro-anatomical distribution, modulating brain regions with different functions in responses to aversive stimuli. Third, endocannabinoids regulate the release of other neurotransmitters that may have even opposing functions, such as GABA and glutamate. Further understanding of the temporal, spatial and functional characteristics of this system is necessary to clarify its role in emotional responses and will promote advances in its therapeutic exploitation.

Addiction Biology • June 2008

Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond

By R.G. Pertwee

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK
rgp@abdn.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/18482430>

A major finding—that (-)-trans-Delta(9)-tetrahydrocannabinol (Delta(9)-THC) is largely responsible for the psychotropic effects of cannabis—prompted research in the 1970s and 1980s that led to the discovery that this plant cannabinoid acts through at least two types of cannabinoid receptor, CB(1) and CB(2), and that Delta(9)-THC and other compounds that target either or both of these receptors as agonists or antagonists have important therapeutic applications. It also led to the discovery that mammalian tissues can themselves synthesize and release agonists for cannabinoid receptors, the first of these to be discovered being arachidonylethanolamide (anandamide) and 2-arachidonoylglycerol. These 'endocannabinoids' are released onto their receptors in a manner that appears to maintain homeostasis within the central nervous system and sometimes either to oppose or to mediate or exacerbate the unwanted effects of certain disorders. This review provides an overview of the pharmacology of cannabinoid receptors and their ligands. It also describes actual and potential clinical uses both for cannabinoid receptor agonists and antagonists and for compounds that affect the activation of cannabinoid receptors less directly, for example by inhibiting the enzymatic hydrolysis of endocannabinoids following their release.

Addiction Biology • June 2008

Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure

By M. Schneider

Central Institute of Mental Health (ZI), Department of Psychopharmacology, Mannheim, Germany
miriam.schneider@zi-mannheim.de

<http://www.ncbi.nlm.nih.gov/pubmed/18482434>

During puberty, neuronal maturation of the brain, which began during perinatal development, is completed such that the behavioral potential of the adult organism can be fully achieved. These maturational events and processes of reorganization are needed for the occurrence of adult behavioral performance but simultaneously render the organism highly susceptible to perturbations, such as exposure to psychoactive drugs, during this critical developmental time span. Considering the variety of maturational processes occurring in the endocannabinoid system during this critical period, it is not surprising that the still-developing brain might be highly susceptible to cannabis exposure. Emerging evidence from human studies and animal research demonstrates that an early onset of cannabis consumption might have lasting consequences on cognition, might increase the risk for neuropsychiatric disorders, promote further illegal drug intake and increase the likelihood of cannabis dependence. These findings suggest that young people represent a highly vulnerable cannabis consumer group and that they run a higher risk than adult consumers of suffering from adverse consequences from cannabinoid exposure. The aim of the present review is to provide an overview over the possible deleterious residual cannabinoid effects during critical periods of postnatal maturation and to offer a more precise delineation of the vulnerable time window for cannabinoid exposure.

Regional brain abnormalities associated with long-term heavy cannabis use

Yücel M1, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, Lubman DI.

MAPS, ORYGEN Research Centre, 35 Poplar Rd, Melbourne, Victoria, Australia
murat@unimelb.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/21982932>

Cannabis is the most widely used illicit drug in the developed world. Despite this, there is a paucity of research examining its long-term effect on the human brain.

Participants were recruited from the general community and underwent imaging at a hospital research facility.

Fifteen carefully selected long-term (>10 years) and heavy (>5 joints daily) cannabis-using men (mean age, 39.8 years; mean duration of regular use, 19.7 years) with no history of polydrug abuse or neurologic/mental disorder and 16 matched nonusing control subjects (mean age, 36.4 years).

Cannabis users had bilaterally reduced hippocampal and amygdala volumes ($P = .001$), with a relatively (and significantly [$P = .02$]) greater magnitude of reduction in the former (12.0% vs 7.1%). Left hemisphere hippocampal volume was inversely associated with cumulative exposure to cannabis during the previous 10 years ($P = .01$) and subthreshold positive psychotic symptoms ($P < .001$). Positive symptom scores were also associated with cumulative exposure to cannabis ($P = .048$). Although cannabis users performed significantly worse than controls on verbal learning ($P < .001$), this did not correlate with regional brain volumes in either group.

These results provide new evidence of exposure-related structural abnormalities in the hippocampus and amygdala in long-term heavy cannabis users and corroborate similar findings in the animal literature. These findings indicate that heavy daily cannabis use across protracted periods exerts harmful effects on brain tissue and mental health.

Multiple roles for the endocannabinoid system during the earliest stages of life: pre- and postnatal development

By E. Fride

Department of Behavioural Sciences, Ariel University Center of Samaria, Ariel, Israel
fride@ariel.ac.il

<http://www.ncbi.nlm.nih.gov/pubmed/18426504>

The endocannabinoid system, including its receptors (CB(1) and CB(2)), endogenous ligands ('endocannabinoids'), synthesising and degrading enzymes, as well as transporter molecules, has been detected from the earliest stages of embryonic development and throughout pre- and postnatal development. In addition, the endocannabinoids, notably 2-arachidonyl glycerol, are also present in maternal milk. During three distinct developmental stages (i.e. embryonic implantation, prenatal brain development and postnatal suckling), the endocannabinoid system appears to play an essential role for development and survival. Thus, during early pregnancy, successful embryonic passage through the oviduct and implantation into the uterus both require critical enzymatic control of optimal anandamide levels at the appropriate times and sites. During foetal life, the cannabinoid CB(1) receptor plays a major role in brain development, regulating neural progenitor differentiation into neurones and glia and guiding axonal migration and synaptogenesis. Postnatally, CB(1) receptor blockade interferes with the initiation of milk suckling in mouse pups, by

inducing oral motor weakness, which exposes a critical role for CB(1) receptors in the initiation of milk suckling by neonates, possibly by interfering with innervation of the tongue muscles. Manipulating the endocannabinoid system by pre- and/or postnatal administration of cannabinoids or maternal marijuana consumption, has significant, yet subtle effects on the offspring. Thus, alterations in the dopamine, GABA and endocannabinoid systems have been reported while enhanced drug seeking behaviour and impaired executive (prefrontal cortical) function have also been observed. The relatively mild nature of the disruptive effects of prenatal cannabinoids may be understood in the framework of the intricate timing requirements and frequently biphasic effects of the (endo)cannabinoids. In conclusion, the endocannabinoid system plays several key roles in pre- and postnatal development. Future studies should further clarify the mechanisms involved and provide a better understanding of the adverse effects of prenatal exposure, in order to design strategies for the treatment of conditions such as infertility, mental retardation and failure-to-thrive.

Cannabis and the developing brain: insights from behavior

Trezza V1, Cuomo V, Vanderschuren LJ.

1. Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Center Utrecht, Utrecht, The Netherlands
vtrezza@umcutrecht.nl

<http://www.ncbi.nlm.nih.gov/pubmed/18413273>

The isolation and identification, in 1964, of delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, opened the door to a whole new field of medical research. The exploration of the therapeutic potential of THC and other natural and synthetic cannabinoid compounds was paralleled by the discovery of the endocannabinoid system, comprising cannabinoid receptors and their endogenous ligands, which offered exciting new insights into brain function. Besides its well-known involvement in specific brain functions, such as control of movement, memory and emotions, the endocannabinoid system plays an important role in fundamental developmental processes such as cell proliferation, migration and differentiation. For this reason, changes in its activity during stages of high neuronal plasticity, such as the perinatal and the adolescent period, can have long-lasting neurobehavioral consequences. Here, we summarize human and animal studies examining the behavioral and neurobiological effects of in utero and adolescent exposure to cannabis. Since cannabis preparations are widely used and abused by young people, including pregnant women, understanding how cannabinoid compounds affect the developing brain, leading to neurobehavioral alterations or neuropsychiatric disorders later in life, is a serious health issue. In addition, since the endocannabinoid system is emerging as a novel therapeutic target for the treatment of several neuropsychiatric diseases, a detailed investigation of possible adverse effects of cannabinoid compounds on the central nervous system (CNS) of immature individuals is warranted.

Molecular And Cellular Endocrinology • April 2008

Long lasting consequences of cannabis exposure in adolescence

Rubino T1, Parolaro D.

1. DBSF and Neuroscience Center, University of Insubria, via A. da Giussano 10, Busto Arsizio (VA), Italy

<http://www.ncbi.nlm.nih.gov/pubmed/18358595>

Despite the increasing use of cannabis among adolescents, there are little and often contradictory studies on the long-term neurobiological consequences of cannabis consumption in juveniles. Adolescence is a critical phase for cerebral development, where the endocannabinoid system plays an important role influencing the release and action of different neurotransmitters. Therefore, a strong stimulation by the psychoactive component of marijuana, delta-9-tetrahydrocannabinol (THC), might lead to subtle but lasting neurobiological changes that can affect adult brain functions and behaviour. The literature here summarized by use of experimental animal models, puts forward that heavy cannabis consumption in adolescence may induce subtle changes in the adult brain circuits ending in altered emotional and cognitive performance, enhanced vulnerability for the use of more harmful drugs of abuse in selected individuals, and may represent a risk factor for developing schizophrenia in adulthood. Therefore, the potential problems arising in relation to marijuana consumption in adolescence suggest that this developmental phase is a vulnerable period for persistent adverse effects of cannabinoids.

European Journal Of Pharmacology • March 2008

Involvement of central cannabinoid CB2 receptor in reducing mechanical allodynia in a mouse model of neuropathic pain

Yamamoto W1, Mikami T, Iwamura H.

Discovery Biology Research, Nagoya Laboratories, Pfizer Global Research and Development, Pfizer Inc., 5-2, Taketoyo, Aichi 470-2393, Japan

<http://www.ncbi.nlm.nih.gov/pubmed/18279850>

We sought to examine the involvement of central cannabinoid CB2 receptor activation in modulating mechanical allodynia in a mouse model of neuropathic pain. JWH133 was demonstrated to be a selective cannabinoid CB2 receptor agonist in mice, reducing forskolin-stimulated cAMP production in CHO cells expressing mouse cannabinoid CB2 and cannabinoid CB1 receptors with EC50 values of 63 nM and 2500 nM, respectively. Intrathecal administration of JWH133 (50 and 100 nmol/mouse) significantly reversed partial sciatic nerve ligation-induced mechanical allodynia in mice at 0.5 h after administration. In contrast, systemic (intraperitoneal) or local (injected to the dorsal surface of the hindpaw) administration of JWH133 (100 nmol/mouse) was ineffective. Furthermore, the analgesic effects of intrathecal JWH133 (100 nmol/mouse) were absent in cannabinoid CB2 receptor knockout mice. These results suggest that the activation of central, but not peripheral, cannabinoid CB2 receptors play an important role in reducing mechanical allodynia in a mouse model of neuropathic pain.

American Journal Of Addiction • March 2008

**The association between earlier marijuana use
and subsequent academic achievement and health problems: a longitudinal study**

Brook JS1, Stimmel MA, Zhang C, Brook DW.

Department of Psychiatry, New York University School of Medicine, New York, New York 10016, USA
Judith.brook@med.nyu.edu

Full text with 31 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3638839/>

In this prospective longitudinal study, the authors investigated the association between marijuana use over a period of 13 years and subsequent health problems at age 27. A community sample of 749 participants from upstate New York was interviewed at mean ages of 14, 16, 22, and 27 years. Marijuana use over time was significantly associated with increased health problems by the late twenties, including respiratory problems, general malaise, neurocognitive problems, and lower academic achievement and functioning. Effective prevention and intervention programs should consider the wide range of adverse physiological and psychosocial outcomes associated with marijuana use over time.

Prenatal marijuana exposure and intelligence test performance at age 6

Goldschmidt L1, Richardson GA, Willford J, Day NL.

1. University of Pittsburgh Medical Center, PA, USA
Lidush@pitt.edu

<http://www.ncbi.nlm.nih.gov/pubmed/18216735>

This is a prospective study of the effects of prenatal marijuana exposure on the intelligence test performance of 648 children at a 6-year follow-up.

Women were interviewed about the amount and frequency of their marijuana use at 4 and 7 months of pregnancy and at delivery. Participants were light to moderate users of marijuana and represented a lower income population. Children were assessed with the Stanford-Binet Intelligence Scale by examiners blind to exposure status. Multiple regression was applied to examine the effects of prenatal marijuana exposure on children's intelligence after partialing out the effects of other significant predictors.

There was a significant nonlinear relationship between marijuana exposure and child intelligence. Heavy marijuana use (one or more cigarettes per day) during the first trimester was associated with lower verbal reasoning scores on the Stanford-Binet Intelligence Scale. Heavy use during the second trimester predicted deficits in the composite, short-term memory, and quantitative scores. Third-trimester heavy use was negatively associated with the quantitative score. Other significant predictors of intelligence included maternal IQ, home environment, and social support.

These findings indicate that prenatal marijuana exposure has a significant effect on school-age intellectual development.

The endocannabinoid system and multiple sclerosis

Baker D1, Pryce G.

1. Neuroimmunology Unit, Neuroscience Centre, Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, 4 Newark Street, London E12AT, UK
david.baker@qmul.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/18781983>

Multiple sclerosis (MS) is a neurodegenerative disease that is characterised by repeated inflammatory/demyelinating events within the central nervous system (CNS). In addition to relapsing-remitting neurological insults, leading to loss of function, patients are often left with residual, troublesome symptoms such as spasticity and pain. These greatly diminish "quality of life" and have prompted some patients to self-medicate with and perceive benefit from cannabis. Recent advances in cannabinoid biology are beginning to support these anecdotal observations, notably the demonstration that spasticity is tonically regulated by the endogenous cannabinoid system. Recent clinical trials may indeed suggest that cannabis has some potential to relieve, pain, spasms and spasticity in MS. However, because the CB(1) cannabinoid receptor mediates both the positive and adverse effects of cannabis, therapy will invariably be associated with some unwanted, psychoactive effects. In an experimental model of MS, and in MS tissue, there are local perturbations of the endocannabinoid system in lesional areas. Stimulation of endocannabinoid activity in these areas either through increase of synthesis or inhibition of endocannabinoid degradation offers the positive therapeutic potential of the cannabinoid system whilst limiting adverse events by locally targeting the lesion. In addition, CB(1) and CB(2) cannabinoid receptor stimulation may also have anti-inflammatory and neuroprotective potential as the endocannabinoid system controls the level of neurodegeneration that occurs as a result of the inflammatory insults. Therefore cannabinoids may not only offer symptom control but may also slow the neurodegenerative disease progression that ultimately leads to the accumulation of disability.

Cannabinoids desensitize capsaicin and mustard oil responses in sensory neurons via TRPA1 activation

Akopian AN1, Ruparel NB, Patwardhan A, Hargreaves KM.

1. Department of Endodontics, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229, USA
akopian@uthscsa.edu

Full text, PDF, with 80 references

<http://www.jneurosci.org/content/28/5/1064.full.pdf+html>

Although the cannabinoid agonists R-(+)-(2,3-dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrolo[1,2,3-de]-1,4-benzoxazin-6-yl)-(1-naphthalenyl) methanone mesylate [WIN 55,212-2 (WIN)] and (R,S)-3-(2-iodo-5-nitrobenzoyl)-1-(1-methyl-2-piperidinylmethyl)-1H-indole (AM1241) exert peripheral antihyperalgesia in inflammatory pain models, the mechanism for cannabinoid-induced inhibition of nociceptive sensory neurons has not been fully studied.

Together, this study demonstrates that certain cannabinoids exert their peripheral antinocifensive actions via activation of the TRPA1 channel on sensory neurons.

Expert Reviews In Neurotherapy • January 2008

Cannabinoids as potential new therapy for the treatment of gliomas

Parolaro D1, Massi P.

1. Department of Structural & Functional Biology, Pharmacology Section, Center of Neuroscience, University of Insubria, Via A da Giussano 10, Busto Arsizio (VA), Italy
daniela.parolaro@uninsubria.it

<http://www.ncbi.nlm.nih.gov/pubmed/18088200>

Gliomas constitute the most frequent and malignant primary brain tumors. Current standard therapeutic strategies (surgery, radiotherapy and chemotherapeutics, e.g., temozolomide, carmustin or carboplatin) for their treatment are only palliative and survival diagnosis is normally 6-12 months. The development of new therapeutic strategies for the management of gliomas is therefore essential. Interestingly, cannabinoids have been shown to exert antiproliferative effects on a wide spectrum of cells in culture. Of interest, cannabinoids have displayed a great potency in reducing glioma tumor growth either in vitro or in animal experimental models, curbing the growth of xenografts generated by subcutaneous or intratecal injection of glioma cells in immune-deficient mice. Moreover, cannabinoids appear to be selective antitumoral agents as they kill glioma cells without affecting the viability of nontransformed counterparts. A pilot clinical trial on patients with glioblastoma multiforme demonstrated their good safety profile together and remarkable antitumor effects, and may set the basis for further studies aimed at better evaluating the potential anticancer activity of cannabinoids.

The influence of marijuana use on neurocognitive functioning in adolescents

Schweinsburg AD1, Brown SA, Tapert SF.

1. VA San Diego Healthcare System, CA, USA

<http://www.ncbi.nlm.nih.gov/pubmed/19630709>

Marijuana use is common in adolescence, yet neural consequences have not been well delineated. This review seeks to ascertain whether heavy marijuana use in adolescence is associated with persistent neurocognitive abnormalities, and whether adolescents are more vulnerable to the impact of chronic marijuana use than adults. Among heavy marijuana using adults, neurocognitive deficits are apparent for several days following use, but may disappear after one month of abstinence. Studies of adolescent heavy users have identified impairments in learning and working memory up to six weeks after cessation, suggesting persisting effects, yet raise the possibility that abnormalities may remit with a longer duration of abstinence. Given ongoing neuromaturation during youth, adolescents may be more vulnerable to potential consequences of marijuana use than adults. This is supported by rodent models, which show greater memory impairments in animals exposed to cannabinoids as adolescents relative to those exposed as adults. Further, adult humans who initiated use in early adolescence show greater dysfunction than those who began use later. Together, these results suggest that adolescents are more vulnerable than adults to neurocognitive abnormalities associated with chronic heavy marijuana use; however, the impact of preexisting risk factors is unknown. Adolescents demonstrate persisting deficits related to heavy marijuana use for at least six weeks following discontinuation, particularly in the domains of learning, memory, and working memory. Further, adolescents appear more adversely affected by heavy use than adults. Longitudinal studies will help ascertain whether preexisting differences contribute to these abnormalities.

Dialogues In Clinical Neuroscience • December 2007

Cannabinoids in health and disease

Kogan NM1, Mechoulam R.

Full text with 278 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202504/>

Cannabis sativa L. preparations have been used in medicine for millenia. However, concern over the dangers of abuse led to the banning of the medicinal use of marijuana in most countries in the 1930s. Only recently, marijuana and individual natural and synthetic cannabinoid receptor agonists and antagonists, as well as chemically related compounds, whose mechanism of action is still obscure, have come back to being considered of therapeutic value. However, their use is highly restricted. Despite the mild addiction to cannabis and the possible enhancement of addiction to other substances of abuse, when combined with cannabis, the therapeutic value of cannabinoids is too high to be put aside. Numerous diseases, such as anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, and metabolic syndrome-related disorders, to name just a few, are being treated or have the potential to be treated by cannabinoid agonists/antagonists/cannabinoid-related compounds. In view of the very low toxicity and the generally benign side effects of this group of compounds, neglecting or denying their clinical potential is unacceptable--instead, we need to work on the development of more selective cannabinoid receptor agonists/antagonists and related compounds, as well as on novel drugs of this family with better selectivity, distribution patterns, and pharmacokinetics, and--in cases where it is impossible to separate the desired clinical action and the psychoactivity--just to monitor these side effects carefully.

Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury

Durst R1, Danenberg H, Gallily R, Mechoulam R, Meir K, Grad E, Beerli R, Pugatsch T, Tarsish E, Lotan C.

Full text with 38 references

<http://ajpheart.physiology.org/content/293/6/H3602>

Cannabidiol (CBD) is a major, nonpsychoactive Cannabis constituent with anti-inflammatory activity mediated by enhancing adenosine signaling. Inasmuch as adenosine receptors are promising pharmaceutical targets for ischemic heart diseases, we tested the effect of CBD on ischemic rat hearts. For the *in vivo* studies, the left anterior descending coronary artery was transiently ligated for 30 min, and the rats were treated for 7 days with CBD (5 mg/kg ip) or vehicle. Cardiac function was studied by echocardiography. Infarcts were examined morphometrically and histologically. For *ex vivo* evaluation, CBD was administered 24 and 1 h before the animals were killed, and hearts were harvested for physiological measurements. *In vivo* studies showed preservation of shortening fraction in CBD-treated animals: from 48 +/- 8 to 39 +/- 8% and from 44 +/- 5 to 32 +/- 9% in CBD-treated and control rats, respectively (n = 14, P < 0.05). Infarct size was reduced by 66% in CBD-treated animals, despite nearly identical areas at risk (9.6 +/- 3.9 and 28.2 +/- 7.0% in CBD and controls, respectively, P < 0.001) and granulation tissue proportion as assessed qualitatively. Infarcts in CBD-treated animals were associated with reduced myocardial inflammation and reduced IL-6 levels (254 +/- 22 and 2,812 +/- 500 pg/ml in CBD and control rats, respectively, P < 0.01). In isolated hearts, no significant difference in infarct size, left ventricular developed pressures during ischemia and reperfusion, or coronary flow could be detected between CBD-treated and control hearts. Our study shows that CBD induces a substantial *in vivo* cardioprotective effect from ischemia that is not observed *ex vivo*. Inasmuch as CBD has previously been administered to humans without causing side effects, it may represent a promising novel treatment for myocardial ischemia.

Alzheimer's disease; taking the edge off with cannabinoids?

Campbell VA1, Gowran A.

1. Department of Physiology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
vacmpbll@tcd.ie

Full text with 87 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190031/>

Alzheimer's disease is an age-related neurodegenerative condition associated with cognitive decline. The pathological hallmarks of the disease are the deposition of beta-amyloid protein and hyperphosphorylation of tau, which evoke neuronal cell death and impair inter-neuronal communication. The disease is also associated with neuroinflammation, excitotoxicity and oxidative stress. In recent years the proclivity of cannabinoids to exert a neuroprotective influence has received substantial interest as a means to mitigate the symptoms of neurodegenerative conditions. In brains obtained from Alzheimer's patients alterations in components of the cannabinoid system have been reported, suggesting that the cannabinoid system either contributes to, or is altered by, the pathophysiology of the disease. Certain cannabinoids can protect neurons from the deleterious effects of beta-amyloid and are capable of reducing tau phosphorylation. The propensity of cannabinoids to reduce beta-amyloid-evoked oxidative stress and neurodegeneration, whilst stimulating neurotrophin expression neurogenesis, are interesting properties that may be beneficial in the treatment of Alzheimer's disease. Delta 9-tetrahydrocannabinol can also inhibit acetylcholinesterase activity and limit amyloidogenesis which may improve cholinergic transmission and delay disease progression. Targeting cannabinoid receptors on microglia may reduce the neuroinflammation that is a feature of Alzheimer's disease, without causing psychoactive effects. Thus, cannabinoids offer a multi-faceted approach for the treatment of Alzheimer's disease by providing neuroprotection and reducing neuroinflammation, whilst simultaneously supporting the brain's intrinsic repair mechanisms by augmenting neurotrophin expression and enhancing neurogenesis. The evidence supporting a potential role for the cannabinoid system as a therapeutic target for the treatment of Alzheimer's disease will be reviewed herewith.

Neuroscientist • October 2007

Functional imaging studies in cannabis users

Chang L1, Chronicle EP.

Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA
LChang@hawaii.edu

<http://www.ncbi.nlm.nih.gov/pubmed/17901252>

Cannabis remains the most widely used illegal drug in the United States. This update examines the available literature on neuroimaging studies of the brains of cannabis users. The majority of studies examining the acute effects of delta-9-tetrahydrocannabinol (THC) administration used PET methods and concluded that administration of THC leads to increased activation in frontal and paralimbic regions and the cerebellum. These increases in activation are broadly consistent with the behavioral effects of the drug. Although there is only equivocal evidence that chronic cannabis use might result in structural brain changes, blood-oxygenation-level-dependent-fMRI studies in chronic users consistently show alterations, or neuroadaptation, in the activation of brain networks responsible for higher cognitive functions. It is not yet certain whether these changes are reversible with abstinence. Given the high prevalence of cannabis use among adolescents, studies are needed to evaluate whether cannabis use might affect the developing brain. Considerable further work, employing longitudinal designs, is also required to determine whether cannabis use causes permanent functional alterations in the brains of adults.

Clinical Therapeutics • September 2007

**Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis:
an uncontrolled, open-label, 2-year extension trial**

Rog DJ1, Nurmikko TJ, Young CA.

Walton Centre for Neurology and Neurosurgery, Liverpool, UK
djrdjr@doctors.org.uk

<http://www.ncbi.nlm.nih.gov/pubmed/18035205>

Central neuropathic pain (CNP), pain initiated or caused by a primary lesion or dysfunction of the central nervous system, occurs in ~28% of patients with multiple sclerosis (MS). Delta(9)-Tetrahydrocannabinol/cannabidiol (THC/CBD), an endocannabinoid system modulator, has demonstrated efficacy for up to 4 weeks in randomized controlled trials in the treatment of CNP in patients with MS.

The purpose of this extension was to establish long-term tolerability and effectiveness profiles for THC/CBD (Sativex (R), GW Pharmaceuticals plc, Salisbury, United Kingdom) oromucosal spray in CNP associated with MS.

THC/CBD was effective, with no evidence of tolerance, in these select patients with central neuropathic pain and multiple sclerosis who completed approximately 2 years of treatment (n = 28). Ninety-two percent of patients experienced an adverse events, the most common of which were dizziness and nausea. The majority of adverse events were deemed to be of mild to moderate severity by the investigators.

Addiction Biology • September 2007

Perinatal exposure to delta-9-tetrahydrocannabinol causes enduring cognitive deficits associated with alteration of cortical gene expression and neurotransmission in rats

Campolongo P1, Trezza V, Cassano T, Gaetani S, Morgese MG, Ubaldi M, Soverchia L, Antonelli T, Ferraro L, Massi M, Ciccocioppo R, Cuomo V.

Department of Human Physiology and Pharmacology, Sapienza, University of Rome, Italy

<http://www.ncbi.nlm.nih.gov/pubmed/17578508>

The aim of the present study was to investigate whether perinatal exposure to a moderate dose of delta-9-tetrahydrocannabinol (THC) alters cortical gene expression and neurotransmission, leading to enduring cognitive dysfunctions in rat offspring. To this purpose, rat dams were treated, from gestational day 15 to postnatal day 9, with THC at a daily dose (5 mg/kg, per os) devoid of overt signs of toxicity. THC did not influence reproduction parameters, whereas it caused subtle neurofunctional deficits in the adult offspring. Particularly, perinatal THC induced long-lasting alterations of cortical genes related to glutamatergic and noradrenergic systems, associated with a decrease in the cortical extracellular levels of both neurotransmitters. These alterations may account, at least in part, for the enduring cognitive impairment displayed by THC-exposed offspring. Taken together, the present results highlight how exposure to cannabinoids during early stages of brain development can lead to irreversible, subtle dysfunctions in the offspring.

Cannabis and Endocannabinoids: 'The Old Man and the Teenagers'

By Didier M. Lambert

Groupe Cannabinoïdes & Endocannabinoïdes, Unité de Chimie pharmaceutique et de Radiopharmacie, Ecole de Pharmacie
Faculté de Médecine, Université catholique de Louvain, Avenue E. Mounier 73, UCL-CMFA 73.40, B-1200 Bruxelles
E-mail address: didier.lambert@uclouvain.be

<http://onlinelibrary.wiley.com/doi/10.1002/cbdv.200790143/pdf>

The title of this Editorial requires some explanation. The main idea of this special issue was to cross two timescales. The one from the plant Cannabis to the cannabinoid receptors started 5,000 years ago – more than five times Methuselah's lifespan – and the second one began in 1992, just the time of adolescence. I was thinking also that, in a single life, scientists were lucky to read three important pages of cannabinoid science: the isolation and structure elucidation of the major psychoactive ingredient in 1964, the characterization of the cannabinoid receptors during the eighties and their cloning in the early nineties, and the discovery of the endocannabinoids starting in 1992 with anandamide. Three pages among others, but without these three pages, the book remains hard to read. This led me to search in the literature the inspiration for the title of this Editorial, and my first thoughts were for the Ernest Hemingway's novel: "The Old Man and the Sea". Of course the Old Man is Cannabis, a plant crossing the humankind history and most of the civilizations. And the Sea is the numerous effects of this plant, featuring advances in the understanding of fundamental mechanisms. But this title was not entirely satisfactory: where is the place of endocannabinoids in the title? So I moved to "The Old Man and the Teenagers", because Teenagers have, of course, still to learn from the Old Man, who was for 5000 years the witness of the evolution of Science. In contrast, it is never too late to learn, even for the Old Man, and the Teenagers in these days of intense technological progress may show the way, for example the use of Web and/or internet by the senior is often due to the teaching of their grandchildren. Similarly, the Teenagers featuring here the numerous endocannabinoids discovered so far, and others to come, open new perspectives either in the fundamental neurobiology or in the understanding of Cannabis and cannabinoids pharmacological and toxicological properties.

Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression

Esposito G1, Scuderi C, Savani C, Steardo L Jr, De Filippis D, Cottone P, Iuvone T, Cuomo V, Steardo L.

Full text with 34 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2189818/>

Pharmacological inhibition of beta-amyloid (A β) induced reactive gliosis may represent a novel rationale to develop drugs able to blunt neuronal damage and slow the course of Alzheimer's disease (AD). Cannabidiol (CBD), the main non-psychotropic natural cannabinoid, exerts in vitro a combination of neuroprotective effects in different models of A β neurotoxicity. The present study, performed in a mouse model of AD-related neuroinflammation, was aimed at confirming in vivo the previously reported antiinflammatory properties of CBD.

Mice were inoculated with human A β (1-42) peptide into the right dorsal hippocampus, and treated daily with vehicle or CBD (2.5 or 10 mg kg⁻¹, i.p.) for 7 days. mRNA for glial fibrillary acidic protein (GFAP) was assessed by in situ hybridization. Protein expression of GFAP, inducible nitric oxide synthase (iNOS) and IL-1 β was determined by immunofluorescence analysis. In addition, ELISA assay of IL-1 β level and the measurement of NO were performed in dissected and homogenized ipsilateral hippocampi, derived from vehicle and A β inoculated mice, in the absence or presence of CBD. In contrast to vehicle, CBD dose-dependently and significantly inhibited GFAP mRNA and protein expression in A β injected animals. Moreover, under the same experimental conditions, CBD impaired iNOS and IL-1 β protein expression, and the related NO and IL-1 β release.

The results of the present study confirm in vivo anti-inflammatory actions of CBD, emphasizing the importance of this compound as a novel promising pharmacological tool capable of attenuating A β evoked neuroinflammatory responses.

Molecular Neurobiology • August 2007

Cannabinoids and gliomas

Velasco G1, Carracedo A, Blázquez C, Lorente M, Aguado T, Haro A, Sánchez C, Galve-Roperh I, Guzmán M.

1. Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040 Madrid, Spain

<http://www.ncbi.nlm.nih.gov/pubmed/17952650>

Cannabinoids, the active components of *Cannabis sativa* L., act in the body by mimicking endogenous substances--the endocannabinoids--that activate specific cell surface receptors. Cannabinoids exert various palliative effects in cancer patients. In addition, cannabinoids inhibit the growth of different types of tumor cells, including glioma cells, in laboratory animals. They do so by modulating key cell signaling pathways, mostly the endoplasmic reticulum stress response, thereby inducing antitumoral actions such as the apoptotic death of tumor cells and the inhibition of tumor angiogenesis. Of interest, cannabinoids seem to be selective antitumoral compounds, as they kill glioma cells, but not their non-transformed astroglial counterparts. On the basis of these preclinical findings, a pilot clinical study of Delta(9)-tetrahydrocannabinol (THC) in patients with recurrent glioblastoma multiforme has been recently run. The good safety profile of THC, together with its possible growth-inhibiting action on tumor cells, justifies the setting up of future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

Chemistry & Biodiversity • August 2007

On the pharmacological properties of Delta9-tetrahydrocannabinol (THC)

By B. Costa

Department of Biotechnology and Bioscience, University of Milano-Bicocca, Piazza della Scienza 2, I-20126 Milano, Italy
barbara.costa@unimib.it

<http://www.ncbi.nlm.nih.gov/pubmed/17712813>

Cannabis is one of the first plants used as medicine, and the notion that it has potentially valuable therapeutic properties is a matter of current debate. The isolation of its main constituent, Delta9-tetrahydrocannabinol (THC), and the discovery of the endocannabinoid system (cannabinoid receptors CB1 and CB2 and their endogenous ligands) made possible studies concerning the pharmacological activity of cannabinoids. This paper reviews some of the most-important findings in the field of THC pharmacology. Clinical trials, anecdotal reports, and experiments employing animal models strongly support the idea that THC and its derivatives exhibit a wide variety of therapeutic applications. However, the psychotropic effects observed in laboratory animals and the adverse reactions reported during human trials, as well as the risk of tolerance development and potential dependence, limit the application of THC in therapy. Nowadays, researchers focus on other therapeutic strategies by which the endocannabinoid system might be modulated to clinical advantage (inhibitor or activator of endocannabinoid biosynthesis, cellular uptake, or metabolism). However, emerging evidence highlights the beneficial effects of the whole cannabis extract over those observed with single components, indicating cannabis-based medicines as new perspective to revisit the pharmacology of this plant.

Molecular Neurobiology • August 2007

The endocannabinoid system and extinction learning

By B. Lutz

Department of Physiological Chemistry, Johannes Gutenberg-University Mainz, Duesbergweg 6, D-55099 Mainz, Germany
blutz@uni-mainz.de

<http://www.ncbi.nlm.nih.gov/pubmed/17952654>

The endocannabinoid system has emerged as a versatile neuromodulatory system, implicated in a plethora of physiological and pathophysiological processes. Cannabinoid receptor type 1 (CB1 receptor) and endocannabinoids are widely distributed in the brain. Their roles in learning and memory have been well documented, using rodents in various memory tests. Depending on the test, the endocannabinoid system is required in the acquisition and/or extinction of memory. In particular, the activation of CB1 receptor-mediated signaling is centrally involved in the facilitation of behavioral adaptation after the acquisition of aversive memories. As several human psychiatric disorders, such as phobia, generalized anxiety disorders, and posttraumatic stress disorder (PTSD) appear to involve aberrant memory processing and impaired adaptation to changed environmental conditions, the hope has been fuelled that the endocannabinoid system might be a valuable therapeutic target for the treatment of these disorders. This review summarizes the current data on the role of the endocannabinoid system in the modulation of extinction learning.

Prevalence of substance use and delinquent behavior in adolescents from Victoria, Australia and Washington State, United States

McMorris BJ¹, Hemphill SA, Toumbourou JW, Catalano RF, Patton GC.

1. University of Washington, Seattle, USA
Barbara.McMorris@i3innovus.com

<http://www.ncbi.nlm.nih.gov/pubmed/16740513>

This article compares prevalence estimates of substance use and delinquent behavior in Washington State, United States and Victoria, Australia, two states chosen for their different policy environments around problem behavior. Few comparisons of international differences on rates of multiple problem behavior exist, and most are based on methods that are not matched, raising the question of whether findings are based on methodological differences rather than actual rate differences. The International Youth Development Study used standardized methods to recruit and administer an adaptation of the Communities That Care Youth Survey to representative state samples of fifth-, seventh-, and ninth-grade students in each state. Rates of delinquent behavior were generally comparable. However, striking differences in substance use were noted, with Victoria students reporting higher rates of alcohol use, alcohol misuse, smoking, and inhalant use, whereas Washington State students reported higher rates of marijuana use. Implications for conducting international comparisons are discussed.

Current Pharmaceutical Biotechnology • August 2007

Recent advances in *Cannabis sativa* research: biosynthetic studies and its potential in biotechnology

Sirikantaramas S1, Taura F, Morimoto S, Shoyama Y.

Graduate School of Pharmaceutical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan

<http://www.ncbi.nlm.nih.gov/pubmed/17691992>

Cannabinoids, consisting of alkylresorcinol and monoterpene groups, are the unique secondary metabolites that are found only in *Cannabis sativa*. Tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabichromene (CBC) are well known cannabinoids and their pharmacological properties have been extensively studied. Recently, biosynthetic pathways of these cannabinoids have been successfully established. Several biosynthetic enzymes including geranylpyrophosphate:olivetolate geranyltransferase, tetrahydrocannabinolic acid (THCA) synthase, cannabidiolic acid (CBDA) synthase and cannabichromenic acid (CBCA) synthase have been purified from young rapidly expanding leaves of *C. sativa*. In addition, molecular cloning, characterization and localization of THCA synthase have been recently reported. THCA and cannabigerolic acid (CBGA), its substrate, were shown to be apoptosis-inducing agents that might play a role in plant defense. Transgenic tobacco hairy roots expressing THCA synthase can produce THCA upon feeding of CBGA. These results open the way for biotechnological production of cannabinoids in the future.

Human cannabinoid pharmacokinetics

By M.A. Huestis

1. Chemistry and Drug Metabolism, Intramural Research Program, National Institute on Drug Abuse, NIH, 5500 Nathan Shock Drive, Baltimore, MD 21146, USA
mhuestis@intra.nida.nih.gov

Full text with 189 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4851925/>

A multitude of roles for the endogenous cannabinoid system has been proposed by recent research efforts. A large number of endogenous cannabinoid neurotransmitters or endocannabinoids have been identified, and the CB-1 and CB-2 cannabinoid receptors have been characterized. The presence of other receptors, transporters, and enzymes responsible for the synthesis or metabolism of endocannabinoids are becoming known at an extraordinary pace. The complex functions of this novel system have created multiple new targets for pharmacotherapies. Research has focused on separating the behavioral psychoactive effects of cannabinoid agonists from therapeutic effects. These efforts have been largely unsuccessful. Another strategy centers on changing the pharmacokinetics of drug delivery to maximize therapeutic effect and minimize cognitive and subjective drug effects. Development of oral, rectal, and transdermal medications of synthetic Δ^9 -tetrahydrocannabinol (THC)¹ are examples of this type of approach. Additionally, the potential therapeutic benefits of administering unique combinations of cannabinoids and other chemicals present in the plant *Cannabis sativa* is being investigated by the oromucosal route. There also is strong interest in medications based on antagonizing endocannabinoid action.

We have shown that the cardiovascular and subjective effects of cannabis are blocked by rimonabant, the first CB-1 cannabinoid-receptor antagonist, documenting that CB-1 receptors mediate these effects of smoked cannabis in humans. It is clear that the endogenous cannabinoid system plays a critical role in physiological and behavioral processes, and extensive research effort is being devoted to the biology, chemistry, pharmacology, and toxicology of cannabinoids.

Cannabis is one of the oldest and most commonly abused drugs in the world, and its use is associated with pathological and behavioral toxicity. Thus, it is important to understand cannabinoid pharmacokinetics and the disposition of cannabinoids into biological fluids and tissues. Understanding the pharmacokinetics of a drug is essential to understanding the onset, magnitude, and duration of its pharmacodynamic effects, maximizing therapeutic and minimizing negative side effects.

Cannabinoid pharmacokinetics encompasses absorption after diverse routes of administration and from different drug formulations, analyte distribution throughout the body, metabolism by the liver and extrahepatic tissues, and elimination in the feces, urine, sweat, oral fluid,

hair. Pharmacokinetic processes are dynamic, may change over time, and may be affected by the frequency and magnitude of drug exposure. The many contributions to our understanding of cannabinoid pharmacokinetics from the 1970s and 1980s are reviewed, and the findings of recent research expanding upon this knowledge are detailed. Cannabinoid pharmacokinetics research is challenging due to low analyte concentrations, rapid and extensive metabolism, and physico-chemical characteristics hindering the separation of drugs of interest from biological matrices and from each other. Drug recovery is reduced due to adsorption of compounds of interest to multiple surfaces. Much of the early cannabinoid data are based on radiolabeled cannabinoids yielding highly sensitive, but less specific, measurement of individual cannabinoid analytes. New extraction techniques and mass-spectrometric (MS) developments now permit highly sensitive and specific measurement of cannabinoids in a wide variety of biological matrices, improving our ability to characterize cannabinoid pharmacokinetics.

Cannabis sativa contains over 421 different chemical compounds, including over 60 cannabinoids [1-3]. Cannabinoid plant chemistry is far more complex than that of pure THC, and different ef-

fects may be expected due to the presence of additional cannabinoids and other chemicals. Eighteen different classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, carbohydrates, terpenes, and simple and fatty acids, contribute to the known pharmacological and toxicological properties of cannabis. THC is usually present in Cannabis plant material as a mixture of monocarboxylic acids, which readily and efficiently decarboxylate upon heating. THC decomposes when exposed to air, heat, or light; exposure to acid can oxidize the compound to cannabinol (CBN), a much less-potent cannabinoid. In addition, cannabis plants dried in the sun release variable amounts of THC through decarboxylation. During smoking, more than 2,000 compounds may be produced by pyrolysis. The pharmacokinetics of THC, the primary psychoactive component of cannabis, its metabolites '11-hydroxytetrahydrocannabinol' (11-OH-THC) and '11-nor-9-carboxy-tetrahydrocannabinol' (THC-COOH)]², and another cannabinoid present in high concentration, cannabidiol (CBD), a non-psychoactive agent with an interesting array of potential therapeutic indications, are included. Mechoulam et al. elucidated the structure of THC in 1964, enabling studies of the drug's pharmacokinetics [4].

Prevalence and correlates of cannabis use in developed and developing countries

Hall W1, Degenhardt L.

1. School of Population Health, University of Queensland, Herston, Queensland, Australia
w.hall@sph.uq.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/17551355>

The aim of this article is to review recent research on the prevalence, antecedents and correlates of cannabis use in young adults in developed and developing countries.

Cannabis is the most widely used illicit drug globally and its use appears to be increasing in developed and developing countries. In developed countries rebelliousness, antisocial behaviour, poor school performance, and affiliation with drug-using peers are risk factors for early and regular cannabis use. Similar antecedents are now being reported in developing countries. Dependence is an underappreciated risk of cannabis that affects one in six to seven adolescents who use cannabis in developed countries. Adolescent cannabis dependence is correlated with an increased risk of using other illicit drugs, symptoms of depression, and symptoms of psychosis. The plausibility of cannabis playing a contributory causal role has increased for symptoms of psychosis in longitudinal studies but remains contentious. In the case of other illicit drug use and mood disorders common causal explanations remain difficult to exclude.

Early and regular cannabis use in adolescence predicts an increased risk of cannabis dependence which in turn predicts an increased risk of using other illicit drugs, and reporting symptoms of mood and psychotic disorders.

Biological Psychiatry • June 2007

Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users

Hermann D1, Sartorius A, Welzel H, Walter S, Skopp G, Ende G, Mann K.

Central Institute of Mental Health, Mannheim, Germany

<http://www.ncbi.nlm.nih.gov/pubmed/17239356>

Cannabinoids present neurotoxic and neuroprotective properties in in vitro studies, inconsistent alterations in human neuroimaging studies, neuropsychological deficits, and an increased risk for psychotic episodes.

Chronic recreational cannabis use is associated with an indication of diminished neuronal and axonal integrity in the dorsolateral prefrontal cortex in this study. As chronic cannabis use is a risk factor for psychosis, these results are interesting because diminished N-acetylaspartate/total creatine ratios in the dorsolateral prefrontal cortex and neuropsychological deficits were also reported in schizophrenia. The strong positive correlation of N-acetylaspartate/total creatine and cannabidiol in the putamen/globus pallidum is in line with neuroprotective properties of cannabidiol, which were also observed in in vitro model studies of Parkinson's disease.

Recent Patents In CNS Drug Discovery • June 2007

The seek of neuroprotection: introducing cannabinoids

Martínez-Orgado J1, Fernández-López D, Lizasoain I, Romero J.

1. Area de Pediatría y Neonatología, Fundación Hospital Alcorcón; Budapest, 1; 28922-Alcorcón Madrid, Spain
jamartinezo@fhacorcon.es

<http://www.ncbi.nlm.nih.gov/pubmed/18221224>

The cannabinoid system is constituted by some endogenous ligands (endocannabinoids), usually arachydonic acid derivatives, and their specific receptors. The endogenous cannabinoid system (ECS) is involved in the control of synaptic transmission, modulating memory, motivation, movement, nociception, appetite and thermoregulation. ECS also exert extraneural effects, mainly immunomodulation and vasodilation. Two cannabinoid receptors have been cloned so far: CB(1) receptors are expressed in the central nervous system (CNS) but can also be found in glial cells and in peripheral tissues; CB(1) receptors are Gi/o protein coupled receptors that modulate the activity of several plasma membrane proteins and intracellular signaling pathways. CB(2) receptors are also Gi/o protein-coupled receptors; although it is accepted that CB(2) receptors are not expressed in forebrain neurons, they have been described in activated glia. Some of the cannabinoids activate other receptors, for instance vanilloid receptors (TRPV1). Lately, the ECS is emerging as a natural system of neuroprotection. This consideration is based on some properties of cannabinoids as their vasodilatory effect, the inhibition of the release of excitotoxic amino acids and cytokines, and the modulation of oxidative stress and toxic production of nitric oxide. Such effects have been demonstrated in adult and newborn animal models of acute and chronic neurodegenerative conditions, and postulate cannabinoids as valuable neuroprotective agents. Patents related to cannabinoid receptors are also discussed.

Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: beyond prevention of acute emesis

By N. E. Slatkin

Department of Supportive Care, Pain and Palliative Medicine, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA 91010, USA
nslatkin@coh.org

<http://www.ncbi.nlm.nih.gov/pubmed/17566383>

Chemotherapy-induced nausea and vomiting (CINV) remains a significant problem in the care of cancer patients. Although the use of serotonin (5-HT₃) receptor antagonists, as well as neurokinin-1 inhibitors, has reduced rates of acute emesis, many patients still experience acute vomiting; moreover, these agents have reduced efficacy in preventing nausea, delayed CINV, and breakthrough CINV. Nausea, in particular, continues to have a major--and often overlooked--impact on patients' quality of life. Optimizing the treatment for CINV likely will involve combinations of agents that inhibit the numerous neurotransmitter systems involved in nausea and vomiting reflexes. Cannabinoids are active in many of these systems, and two oral formulations, dronabinol (Marinol) and nabilone (Cesamet), are approved by the US Food and Drug Administration for use in CINV refractory to conventional antiemetic therapy. Agents in this class have shown superiority to dopamine receptor antagonists in preventing CINV, and there is some evidence that the combination of a dopamine antagonist and cannabinoid is superior to either alone and is particularly effective in preventing nausea. The presence of side effects from the cannabinoids may have slowed their adoption into clinical practice, but in a number of comparative clinical trials, patients have expressed a clear preference for the cannabinoid, choosing its efficacy over any undesired effects. Improvement in antiemetic therapy across the entire spectrum of CINV will involve the use of agents with different mechanisms of action in concurrent or sequential combinations, and the best such combinations should be identified. In this effort, the utility of the cannabinoids should not be overlooked.

Current Opinions In Psychiatry • May 2007

Cannabis use and psychiatric and cognitive disorders: the chicken or the egg?

Di Forti M1, Morrison PD, Butt A, Murray RM.

Department of Psychological Medicine, Institute of Psychiatry, London, UK

<http://www.ncbi.nlm.nih.gov/pubmed/17415074>

Cannabis is the world's most commonly used illicit drug. In this review, we consider the recent literature on the effects of cannabis on mental health and on cognition.

Cannabis use in adolescence increases the risk of later schizophrenia-like psychoses, especially in genetically vulnerable individuals. Not surprisingly, patients already suffering from psychosis who use cannabis have a worse outcome than those who do not. These effects of cannabis may be consequent on its impact on the dopamine system. There is less evidence of cannabis playing an aetiological role in other mental disorders including depression, but there have been far fewer studies. Heavy cannabis use has also been shown to affect memory and learning performance, both in healthy individuals and in patients suffering from psychosis.

Delta9-tetrahydrocannabinol (Delta9-THC) prevents cerebral infarction via hypothalamic-independent hypothermia

Hayakawa K1, Mishima K, Nozako M, Hazekawa M, Ogata A, Fujioka M, Harada K, Mishima S, Orito K, Egashira N, Iwasaki K, Fujiwara M.

1. Department of Neuropharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma 8-19-1, Fukuoka City, Fukuoka, Japan

<http://www.ncbi.nlm.nih.gov/pubmed/17289082>

Delta(9)-tetrahydrocannabinol (Delta(9)-THC), a primary psychoactive constituent of cannabis, has been reported to act as a neuroprotectant via the cannabinoid CB(1) receptor. In this study, Delta(9)-THC significantly decreased the infarct volume in a 4 h mouse middle cerebral artery occlusion mouse model. The neuroprotective effect of Delta(9)-THC was completely abolished by SR141716, cannabinoid CB(1) receptor antagonist, and by warming the animals to 31 degrees C. Delta(9)-THC significantly decreased the rectal temperature, and the hypothermic effect was also inhibited by SR141716 and by warming to 31 degrees C. At 24 h after cerebral ischemia, Delta(9)-THC significantly increased the expression level of CB(1) receptor in both the striatum and cortex, but not in the hypothalamus. Warming to 31 degrees C during 4 h cerebral ischemia did not increase the expression of CB(1) receptor at the striatum and cortex in MCA-occluded mice. These results show that the neuroprotective effect of Delta(9)-THC is mediated by a temperature-dependent mechanism via the CB(1) receptor. In addition, warming to 31 degrees C might attenuate both the neuroprotective and hypothermic effects of Delta(9)-THC through inhibiting the increase in CB(1) receptor in both the striatum and cortex but not in the hypothalamus, which may suggest a new thermoregulation mechanism of Delta(9)-THC.

Repeated treatment with cannabidiol but not Delta9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance

Hayakawa K1, Mishima K, Nozako M, Ogata A, Hazekawa M, Liu AX, Fujioka M, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M.

1. Department of Neuropharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma 8-19-1, Fukuoka City, Fukuoka 814-0180, Japan

<http://www.ncbi.nlm.nih.gov/pubmed/26497782>

Both Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and cannabidiol are known to have a neuroprotective effect against cerebral ischemia. We examined whether repeated treatment with both drugs led to tolerance of their neuroprotective effects in mice subjected to 4h-middle cerebral artery (MCA) occlusion. The neuroprotective effect of Delta(9)-THC but not cannabidiol was inhibited by SR141716, cannabinoid CB(1) receptor antagonist. Fourteen-day repeated treatment with Delta(9)-THC, but not cannabidiol, led to tolerance of the neuroprotective and hypothermic effects. In addition, repeated treatment with Delta(9)-THC reversed the increase in cerebral blood flow (CBF), while cannabidiol did not reverse that effect. Repeated treatment with Delta(9)-THC caused CB(1) receptor desensitization and down-regulation in MCA occluded mice. On the contrary, cannabidiol did not influence these effects. Moreover, the neuroprotective effect and an increase in CBF induced by repeated treatment with cannabidiol were in part inhibited by WAY100135, serotonin 5-HT(1A) receptor antagonist. Cannabidiol exhibited stronger antioxidative power than Delta(9)-THC in an in vitro study using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. Thus, cannabidiol is a potent antioxidant agent without developing tolerance to its neuroprotective effect, acting through a CB(1) receptor-independent mechanism. It is to be hoped that cannabidiol will have a palliative action and open new therapeutic possibilities for treating cerebrovascular disorders.

Tidsskrift for den Norske Lægeforening • March 2007

Cannabis and cannabinoids as drugs

Khiabani HZ1, Mørland J.

1. Nasjonalt folkehelseinstitutt, Divisjon for retts toksikologi og rusmiddelforskning, Postboks 4404 Nydalen, 0403 Oslo
hassan.khiabani@fhi.no

Full text in Norwegian with 55 references

<http://tidsskriftet.no/article/1495645>

Cannabis has been used throughout human history. Delta (9)-tetrahydrocannabinol (THC) is the primary psychoactive component of cannabis. THC metabolises to 11-OH-THC and further to THC-acid, which is an inactive metabolite. We present an overview of the pharmacokinetics and pharmacodynamics of cannabinoids.

It has been demonstrated that mammalian tissues express cannabinoid receptors (CB1, CB2 and most probably CB3) and endogenous ligands for these. Knowledge of these receptors has led to the development of components that stimulate (CB-agonists) or block their function (CB-antagonists). This opens up for the study of any potential therapeutic effects of cannabinoids. Research on a possible therapeutic potential of cannabinoids should however not overshadow the well-documented negative effects of cannabis; i.e. impaired cognitive functions, intoxication and an increased risk for development of psychosis and psychotic symptoms.

Trends In Pharmacological Sciences • February 2007

The emerging functions of endocannabinoid signaling during CNS development

Harkany T1, Guzmán M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K.

1. Division of Molecular Neurobiology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm SE-17177, Sweden
tibor.harkany@ki.se

<http://www.ncbi.nlm.nih.gov/pubmed/17222464>

In the postnatal brain, endocannabinoids acting as retrograde messengers regulate the function of many synapses. By contrast, the understanding of endocannabinoid functions that regulate fundamental developmental processes such as cell proliferation, migration, differentiation and survival during patterning of the CNS is just beginning to unfold. Increasing the knowledge of basic developmental and signaling principles that are controlled by endocannabinoids will provide important insights into the molecular mechanisms that establish functional neuronal circuits in the brain. Moreover, determining the molecular basis of permanent modifications to cellular structure and intercellular communication imposed by cannabis smoking during pregnancy will provide novel therapeutic targets for alleviating pathogenic changes in affected offspring. Here, we summarize recent findings regarding the ontogeny of the endocannabinoid system in neurons that sculpt the temporal and spatial diversity of cellular functions during CNS development.

European Journal Of Pharmacology • February 2007

The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain

Costa B1, Trovato AE, Comelli F, Giagnoni G, Colleoni M.

1. Department of Biotechnology and Bioscience, University of Milano-Bicocca, piazza della Scienza 2, 20126 Milano, Italy
barbara.costa@unimib.it

<http://www.ncbi.nlm.nih.gov/pubmed/17157290>

Cannabidiol, the major psycho-inactive component of cannabis, has substantial anti-inflammatory and immunomodulatory effects. This study investigated its therapeutic potential on neuropathic (sciatic nerve chronic constriction) and inflammatory pain (complete Freund's adjuvant intraplantar injection) in rats. In both models, daily oral treatment with cannabidiol (2.5-20 mg/kg to neuropathic and 20 mg/kg to adjuvant-injected rats) from day 7 to day 14 after the injury, or intraplantar injection, reduced hyperalgesia to thermal and mechanical stimuli. In the neuropathic animals, the anti-hyperalgesic effect of cannabidiol (20 mg/kg) was prevented by the vanilloid antagonist capsazepine (10 mg/kg, i.p.), but not by cannabinoid receptor antagonists. Cannabidiol's activity was associated with a reduction in the content of several mediators, such as prostaglandin E(2) (PGE(2)), lipid peroxide and nitric oxide (NO), and in the over-activity of glutathione-related enzymes. Cannabidiol only reduced the over-expression of constitutive endothelial NO synthase (NOS), without significantly affecting the inducible form (iNOS) in inflamed paw tissues. Cannabidiol had no effect on neuronal and iNOS isoforms in injured sciatic nerve. The compound's efficacy on neuropathic pain was not accompanied by any reduction in nuclear factor-kappaB (NF-kappaB) activation and tumor necrosis factor alpha (TNFalpha) content. The results indicate a potential for therapeutic use of cannabidiol in chronic painful states.

Anandamide regulates postnatal development of long-term synaptic plasticity in the rat dorsolateral striatum

Ade KK1, Lovinger DM.

1. Department of Physiology and Biophysics, Georgetown University School of Medicine, Washington, DC 20007, USA

<http://www.ncbi.nlm.nih.gov/pubmed/17329438>

Long-term changes in synaptic efficacy produced by high-frequency stimulation (HFS) of glutamatergic afferents to the rat dorsolateral striatum exhibit heterogeneity during early stages of postnatal development. Whereas HFS most often induces striatal long-term potentiation (LTP) in rats postnatal day 12 (P12)-P14, the same stimulation tends to induce long-term depression (LTD) at ages P16-P34. Previous studies have shown that striatal LTD induction depends on retrograde endocannabinoid signaling and activation of the CB1 cannabinoid receptor. It is also known that levels of one of the primary endogenous CB1 receptor agonists, anandamide (AEA), increases during development in whole-brain samples. In the present study, we sought to determine whether this developmental increase in AEA also takes place in striatal tissue and whether increased AEA levels contribute to the postnatal switch in the response to HFS. We observed a pronounced increase in striatal levels of AEA, but not the other major endogenous cannabinoid 2-arachidonoylglycerol (2-AG), during the postnatal period characterized by the switch from LTP to LTD. Furthermore, application of synthetic AEA during HFS in field recordings of slices from P12-P14 rats allowed for induction of LTD whereas blocking the CB1 receptor during HFS in animals P16-P34 resulted in expression of LTP. However, blocking 2-AG synthesis with the DAG-lipase inhibitor tetrahydrolipstatin did not alter HFS-induced striatal LTD. In addition, synaptic depression produced by a synthetic CB1 agonist was similar across development. Together, these findings suggest that the robust developmental increase in striatal AEA may be the key factor in the emergence of HFS-induced striatal LTD.

Current Medical Research Opinions • January 2007

Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain

Iskedjian M1, Bereza B, Gordon A, Piwko C, Einarson TR.

1. PharmIdeas Research & Consulting Inc., Oakville, ON, Canada.

<http://www.ncbi.nlm.nih.gov/pubmed/17257464>

Debilitating pain, occurring in 50-70% of multiple sclerosis (MS) patients, is poorly understood and infrequently studied. We summarized efficacy and safety data of cannabinoid-based drugs for neuropathic pain.

Cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in Multiple Sclerosis.

This review was based on a small number of trials and patients. Pain related to MS was assumed to be similar to neuropathic pain.

The acute effects of cannabinoids on memory in humans: a review

Ranganathan M1, D'Souza DC.

Schizophrenia Biological Research Center, VA Connecticut Healthcare System, West-Haven, CT 06516, USA

<http://www.ncbi.nlm.nih.gov/pubmed/17019571>

Cannabis is one of the most frequently used substances. Cannabis and its constituent cannabinoids are known to impair several aspects of cognitive function, with the most robust effects on short-term episodic and working memory in humans. A large body of the work in this area occurred in the 1970s before the discovery of cannabinoid receptors. Recent advances in the knowledge of cannabinoid receptors' function have rekindled interest in examining effects of exogenous cannabinoids on memory and in understanding the mechanism of these effects.

Acute administration of Delta-9-THC transiently impairs immediate and delayed free recall of information presented after, but not before, drug administration in a dose- and delay-dependent manner. In particular, cannabinoids increase intrusion errors. These effects are more robust with the inhaled and intravenous route and correspond to peak drug levels.

This profile of effects suggests that cannabinoids impair all stages of memory including encoding, consolidation, and retrieval. Several mechanisms, including effects on long-term potentiation and long-term depression and the inhibition of neurotransmitter (GABA, glutamate, acetyl choline, dopamine) release, have been implicated in the amnesic effects of cannabinoids. Future research in humans is necessary to characterize the neuroanatomical and neurochemical basis of the memory impairing effects of cannabinoids, to dissect out their effects on the various stages of memory and to bridge the expanding gap between the humans and preclinical literature.

Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis

Wade DT1, Makela PM, House H, Bateman C, Robson P.

Oxford Centre for Enablement, Windmill Road, Oxford OX3 7LD, UK
derick.wade@noc.anglox.nhs.uk

<http://www.ncbi.nlm.nih.gov/pubmed/17086911>

The object of this study was to monitor the safety and efficacy of long-term use of an oromucosal cannabis-based medicine (CBM) in patients with multiple sclerosis (MS). A total of 137 MS patients with symptoms not controlled satisfactorily using standard drugs entered this open-label trial following a 10-week, placebo-controlled study. Patients were assessed every eight weeks using visual analogue scales and diary scores of main symptoms, and were followed for an average of 434 days (range: 21 -814). A total of 58 patients (42.3%) withdrew due to lack of efficacy (24); adverse events (17); withdrew consent (6); lost to follow-up (3); and other (8). Patients reported 292 unwanted effects, of which 251 (86%) were mild to moderate, including oral pain (28), dizziness (20), diarrhoea (17), nausea (15) and oromucosal disorder (12). Three patients had five 'serious adverse events' between them--two seizures, one fall, one aspiration pneumonia, one gastroenteritis. Four patients had first-ever seizures. The improvements recorded and dosage taken in the acute study remained stable. Planned, sudden interruption of CBM for two weeks in 25 patients (of 62 approached) did not cause a consistent withdrawal syndrome, although 11(46%) patients reported at least one of--tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional lability, intoxication or vivid dreams. Twenty-two (88%) patients re-started CBM treatment. We conclude that long-term use of an oromucosal CBM (Sativex) maintains its effect in those patients who perceive initial benefit. The precise nature and rate of risks with long-term use, especially epilepsy, will require larger and longer-term studies.

Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study

Hashibe M1, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, Mack TM, Greenland S.

1. IARC, Lyon, France

Full text with 38 references

Despite several lines of evidence suggesting the biological plausibility of marijuana being carcinogenic, epidemiologic findings are inconsistent. We conducted a population-based case-control study of the association between marijuana use and the risk of lung and upper aerodigestive tract cancers in Los Angeles.

Our study included 1,212 incident cancer cases and 1,040 cancer-free controls matched to cases on age, gender, and neighborhood. Subjects were interviewed with a standardized questionnaire. The cumulative use of marijuana was expressed in joint-years, where 1 joint-year is equivalent to smoking one joint per day for 1 year.

Although using marijuana for ≥ 30 joint-years was positively associated in the crude analyses with each cancer type (except pharyngeal cancer), no positive associations were observed when adjusting for several confounders including cigarette smoking. The adjusted odds ratio estimate (and 95% confidence limits) for ≥ 60 versus 0 joint-years was 1.1 (0.56, 2.1) for oral cancer, 0.84 (0.28, 2.5) for laryngeal cancer, and 0.62 (0.32, 1.2) for lung cancer; the adjusted odds ratio estimate for ≥ 30 versus 0 joint-years was 0.57 (0.20, 1.6) for pharyngeal cancer, and 0.53 (0.22, 1.3) for esophageal cancer. No association was consistently monotonic across exposure categories, and restriction to subjects who never smoked cigarettes yielded similar findings.

Our results may have been affected by selection bias or error in measuring lifetime exposure and confounder histories; but they suggest that the association of these cancers with marijuana, even long-term or heavy use, is not strong and may be below practically detectable limits.

Molecular Pharmacology • September 2006

**Cannabidiol-induced apoptosis in human leukemia cells:
A novel role of cannabidiol in the regulation of p22phox and Nox4 expression**

McKallip RJ1, Jia W, Schlomer J, Warren JW, Nagarkatti PS, Nagarkatti M.

Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, 6439 Garner's Ferry Road, Columbia, SC 29209, USA
rmckallip@gw.med.sc.edu

Full text with 36 references

<http://molpharm.aspetjournals.org/content/70/3/897.long>

In the current study, we examined the effects of the nonpsychoactive cannabinoid, cannabidiol, on the induction of apoptosis in leukemia cells. Together, the results from this study reveal that cannabidiol, acting through CB2 and regulation of Nox4 and p22(phox) expression, may be a novel and highly selective treatment for leukemia.

The endocannabinoid system as an emerging target of pharmacotherapy

Pacher P1, Bátkai S, Kunos G.

1. Laboratory of Physiological Studies, National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892-9413, USA

Full text with 1,332 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241751/>

The recent identification of cannabinoid receptors and their endogenous lipid ligands has triggered an exponential growth of studies exploring the endocannabinoid system and its regulatory functions in health and disease. Such studies have been greatly facilitated by the introduction of selective cannabinoid receptor antagonists and inhibitors of endocannabinoid metabolism and transport, as well as mice deficient in cannabinoid receptors or the endocannabinoid-degrading enzyme fatty acid amidohydrolase. In the past decade, the endocannabinoid system has been implicated in a growing number of physiological functions, both in the central and peripheral nervous systems and in peripheral organs. More importantly, modulating the activity of the endocannabinoid system turned out to hold therapeutic promise in a wide range of disparate diseases and pathological conditions, ranging from mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's disease, neuropathic pain, multiple sclerosis and spinal cord injury, to cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, and osteoporosis, to name just a few. An impediment to the development of cannabinoid medications has been the socially unacceptable psychoactive properties of plant-derived or synthetic agonists, mediated by CB(1) receptors. However, this problem does not arise when the therapeutic aim is achieved by treatment with a CB(1) receptor antagonist, such as in obesity, and may also be absent when the action of endocannabinoids is enhanced indirectly through blocking their metabolism or transport. The use of selective CB(2) receptor agonists, which lack psychoactive properties, could represent another promising avenue for certain conditions. The abuse potential of plant-derived cannabinoids may also be limited through the use of preparations with controlled composition and the careful selection of dose and route of administration. The growing number of preclinical studies and clinical trials with compounds that modulate the endocannabinoid system will probably result in novel therapeutic approaches in a number of diseases for which current treatments do not fully address the patients' need. Here, we provide a comprehensive overview on the current state of knowledge of the endocannabinoid system as a target of pharmacotherapy.

Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14

Day NL1, Goldschmidt L, Thomas CA.

1. Western Psychiatric Institute and Clinic, 1811 O'Hara Street, Pittsburgh, PA 15213, USA
nday@pitt.edu

<http://www.ncbi.nlm.nih.gov/pubmed/16911731>

To evaluate the effects of prenatal marijuana exposure (PME) on the age of onset and frequency of marijuana use while controlling for identified confounds of early marijuana use among 14-year-olds.

In this longitudinal cohort study, women were recruited in their fourth prenatal month. Women and children were followed throughout pregnancy and at multiple time-points into adolescence.

Recruitment was from a hospital-based prenatal clinic. The women ranged in age from 18 to 42, half were African American and half Caucasian, and most were of lower socio-economic status. The women were generally light to moderate substance users during pregnancy and subsequently. At 14 years, 580 of the 763 offspring-mother pairs (76%) were assessed. A total of 563 pairs (74%) was included in this analysis.

Socio-demographic, environmental, psychological, behavioral, biological and developmental factors were assessed. Outcomes were age of onset and frequency of marijuana use at age 14. PME predicted age of onset and frequency of marijuana use among the 14-year-old offspring. This finding was significant after controlling for other variables including the child's current alcohol and tobacco use, pubertal stage, sexual activity, delinquency, peer drug use, family history of drug abuse and characteristics of the home environment including parental depression, current drug use and strictness/supervision.

Prenatal exposure to marijuana, in addition to other factors, is a significant predictor of marijuana use at age 14.

Human Psychopharmacology • June 2006

Cannabis and neurodevelopment: implications for psychiatric disorders

By S. Sundram

Molecular Psychopharmacology, Mental Health Research Institute of Victoria, Australia
ssundram@mhri.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/16783814>

The developing brain is susceptible to the effects of exogenous cannabinoids both during the perinatal period through maternal cannabis use and in young adolescent users. Emerging data from human and animal perinatal exposure studies demonstrate a subtle rather than gross effect of cannabis upon later functioning including; specific cognitive deficits especially in visuospatial function; impulsivity, inattention and hyperactivity; depressive symptoms; and substance use disorders. From animal studies motor control systems, neuroendocrine function and nociception may additionally be affected. Fetal studies indicate that these outcomes may be through cannabinoid mediated influences on the ontogeny of, especially dopamine and opioid, neurotransmitter systems. The effect of cannabinoids in the adolescent suggest long-term deleterious outcomes in cognition, depressive symptoms, schizophrenia and substance use disorders. Much of these data support a neurodevelopmental effect, however, predisposing genetic and/or environmental factors cannot be excluded from human studies. Gender specific differences have been observed in both human and animal studies implying sex hormone and related factors may interact with cannabinoids in neurodevelopment. Further understanding how cannabinoids influence neurodevelopment will inform public debate about the health effects of cannabis but also open avenues in discerning how modulation of the endocannabinoid system may assist in the development of therapeutic tools for a variety of neuropsychiatric disorders.

Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo

Sarafian TA1, Habib N, Oldham M, Seeram N, Lee RP, Lin L, Tashkin DP, Roth MD.

Division of Pulmonary and Critical Care, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1690, USA
tsarafian@mednet.ucla.edu

<http://www.ncbi.nlm.nih.gov/pubmed/16414979>

Habitual marijuana smoking is associated with inflammation and atypia of airway epithelium accompanied by symptoms of chronic bronchitis. We hypothesized that Delta(9)-tetrahydrocannabinol (THC), the primary psychoactive component of marijuana, might contribute to these findings by impairing cellular energetics and mitochondrial function. To test this hypothesis, we examined particulate smoke extracts from marijuana cigarettes, tobacco cigarettes, and placebo marijuana (0% THC) cigarettes for their effects on the mitochondrial function of A549 cells in vitro. Only extracts prepared from marijuana cigarettes altered mitochondrial staining by the potentiometric probe JC-1. With the use of a cross-flow, nose-only inhalation system, rats were then exposed for 20 min to whole marijuana smoke and examined for its effects on airway epithelial cells. Inhalation of marijuana smoke produced lung tissue concentrations of THC that were 8-10 times higher than those measured in blood (75 +/- 38 ng/g wet wt tissue vs. 9.2 +/- 2.0 ng/ml), suggesting high local exposure. Intratracheal infusion of JC-1 immediately following marijuana smoke exposure revealed a diffuse decrease in lung cell JC-1 red fluorescence compared with tissue from unexposed or placebo smoke-exposed rats. Exposure to marijuana smoke in vivo also decreased JC-1 red fluorescence (54% decrease, $P < 0.01$) and ATP levels (75% decrease, $P < 0.01$) in single-cell preparations of tracheal epithelial cells. These results suggest that inhalation of marijuana smoke has deleterious effects on airway epithelial cell energetics that may contribute to the adverse pulmonary consequences of marijuana smoking.

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The genetic epidemiology of cannabis use, abuse and dependence

Agrawal A1, Lynskey MT.

1. Washington University School of Medicine, Department of Psychiatry, St Louis, MO 63110, USA
arana@wustl.edu

<http://www.ncbi.nlm.nih.gov/pubmed/16696624>

The genetic etiology of cannabis use, abuse and dependence has elicited significant interest from genetic epidemiologists.

The substantial evidence for the heritability of cannabis use, abuse and dependence underscore the importance of linkage and association studies that aim to find genes of etiologic significance.

History of cannabis as a medicine: a review

By A.W. Zuardi

Department of Neurology, Psychiatry and Medical Psychology, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, SP, Brazil
awzuardi@fmrp.usp.br

Full text with 29 references

http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-44462006000200015&lng=en&nrm=iso&tlng=en

Cannabis as a medicine was used before the Christian era in Asia, mainly in India. The introduction of cannabis in the Western medicine occurred in the midst of the 19th century, reaching the climax in the last decade of that century, with the availability and usage of cannabis extracts or tinctures. In the first decades of the 20th century, the Western medical use of cannabis significantly decreased largely due to difficulties to obtain consistent results from batches of plant material of different potencies. The identification of the chemical structure of cannabis components and the possibility of obtaining its pure constituents were related to a significant increase in scientific interest in such plant, since 1965. This interest was renewed in the 1990's with the description of cannabinoid receptors and the identification of an endogenous cannabinoid system in the brain. A new and more consistent cycle of the use of cannabis derivatives as medication begins, since treatment effectiveness and safety started to be scientifically proven.

Before the Christian Era

Cannabis Sativa (cannabis) is among the earliest plants cultivated by man. The first evidence of the use of cannabis was found in China, where archeological and historical findings indicate that that plant was cultivated for fibers since 4.000 B.C.¹ With the fibers obtained from the cannabis stems, the Chinese manufactured strings, ropes, textiles, and even paper. Textiles and paper made from cannabis were found in the tomb of Emperor Wu (104-87 B.C.), of the Han dynasty.¹

The Chinese also used cannabis fruits as food. These fruits are small (3 to 5 mm), elliptic, smooth, with a hard shell, and contain one single seed. The first evidence of the use of these seeds was found during the Han dynasty (206 B.C. - 220 A.D.). In the beginning of the Christian Era, with the introduction of new cultures, can-

nabis was no longer an important food in China, although, until today, the seeds are still used for making kitchen oil in Nepal.²

The use of cannabis as a medicine by ancient Chinese was reported in the world's oldest pharmacopoeia, the pen-ts'ao ching which was compiled in the first century of this Era, but based on oral traditions passed down from the time of Emperor Shen-Nung, who lived during the years 2.700 B.C. Indications for the use of cannabis included: rheumatic pain, intestinal constipation, disorders of the female reproductive system, malaria, and others.² In the beginning of the Christian Era, Hua T'o, the founder of Chinese surgery (A.D. 110 – 207), used a compound of the plant, taken with wine, to anesthetize patients during surgical operations.¹

The Chinese used mainly the seeds of cannabis for medical purposes;¹ therefore, it may be assumed that they were referring to that part of the plant when describing its medicinal properties. Until today, cannabis seeds continue to be used as a laxative by Chinese physicians.² It is acknowledged that the seeds are practically deficient in D9-tetrahydrocannabinol (D9-THC), which is considered the plant's main active constituent, and is mainly composed of essential fatty acids and proteins. Today some of these fatty acids are considered as having therapeutic effects, such as the g-linoleic acid, whose topical use is recommended for eczema and psoriasis, and its oral use for atherosclerosis, osteoporosis, rheumatoid arthritis, and other inflammatory diseases.³ In China, the medical use of cannabis never reached the importance it did in India.

The first reference to the use of cannabis, as a psychoactive drug, is also in the pen-ts'ao ching, as observed in one of its phrases: ...ma-fen (the fruit of cannabis)... if taken in excess will produce visions of devils ... over a long term, it makes one

communicate with spirits and lightens one's body...⁴ In spite of this reference, there are scarce citations of the use of cannabis as a hallucinogen in ancient Chinese texts. One possible explanation is that such use was probably associated to shamanism, a religion of the people from Central Asia. During the Han dynasty, this religious practice started to decline in China, and became disbelieved and increasingly restricted. Ancient texts rarely mentioned shamanism and, thus, there is no reference to the use of cannabis as a hallucinogen.² Although shamanism became gradually more restricted in China, it was rather common in the Northern nomadic tribes, which may have contributed to the dissemination of cannabis in Central and Western Asia and in India.⁴

In India, the use of cannabis was widely disseminated, both as a medicine and as a recreational drug. Such a broad use may be due to the fact that cannabis maintained a straight association with religion, which assigned sacred virtues to the plant. The Atharva Veda (a collection of sacred texts of unknown author) mentions cannabis as one of five sacred plants, referring to it as a source of happiness, donator of joy and bringer of freedom. Hence, cannabis use became part of numerous religious rituals in that region.²

The plant's psychoactive effects were well-known in India, possibly due to the way it was prepared for use, which included at least three preparations. The weakest type, Bhang, consists of dry leaves from which flowers are carefully removed. A stronger type, Ganja, is prepared with the female-plant's flowers. The strongest of them all is the Charas, made exclusively of the resin that covers female flowers.² These forms of preparation guarantee the presence of active cannabinoids. Currently we know that the plant has secreting hairs that are located mainly on the female-plant's flowers and, in a smaller amount, on the leaves of its superior third. Solitary resin glands most often form at the tips of the trichome stalks. These glands have a considerable amount of active cannabinoids. Breaking the glands liberates the active cannabinoids.⁵

In India, the medical and religious use of cannabis probably began together around 1000 years B.C.⁶ The plant was used for innumerable functions, such as: analgesic (neuralgia, headache, toothache), anticonvulsant (epilepsy, tetanus, rabies), hypnotic, tranquilizer (anxiety, mania, hysteria), anesthetic, anti-inflammatory (rheumatism and other

inflammatory diseases), antibiotic (topical use on skin infections, erysipelas, tuberculosis), antiparasite (internal and external worms), antispasmodic (colic, diarrhea), digestive, appetite stimulant, diuretic, aphrodisiac or anaphrodisiac, antitussive and expectorant (bronchitis, asthma).^{2,6-7}

Furthermore, cannabis was traditionally considered sacred in Tibet, although little has been written about its religious or medicinal use. In Tantric Buddhism, which was developed in the Himalayas, cannabis was used to facilitate meditation.² Though seldom reported, it is believed that the medical use of cannabis in Tibet was intense due to the following reasons: the concepts of Tibetan medicine stem from Hindi medicine; botany was of great importance in its pharmacopoeia; and, finally, cannabis was abundant in that region.²

Evidence suggests that the Assyrians also knew about the psychoactive effects of cannabis and used it as incense since the ninth century B.C.² It is also possible that, before the Christian Era, Assyrians used the plant externally for swellings and bruises, and internally for depression, impotence, arthritis, kidney stones, 'female ailment', and for the 'annulment of witchcraft'.⁷

In Persia, cannabis was also known before the Christian Era.⁶ The Persians knew about the plant's biphasic effect, and made a clear distinction between its initial euphoric and its late dysphoric effects.² In Europe, historical and archeological evidence suggests the presence of cannabis before the Christian Era. It seems the plant was brought by Scythian invaders, who originated from Central Asia and reached close to the Mediterranean. In the year 450 B.C., Herodotus described a Scythian funeral ceremony, and stated that they inhaled the vapors obtained from burning cannabis seeds with ritualistic and euphoric purposes. That description was later confirmed by archeologists who found charred cannabis seeds in Scythian tombs in Siberia and Germany.⁷ Reference to the use of cannabis by the Greeks and the Romans are scarce, suggesting that it was little used by these people.^{2,6} In the beginning of the Christian Era, there are two references of the use of the seed's juice for earache and to drive worms and insects out of the ears.⁷

Beginning of the Christian Era to the 18th century

In this period, the medical use of cannabis remained very intense in India and was then spread to the Middle East and Africa. In Arabia, well-known physicians mentioned cannabis in their medical compendiums, as Avicena, in the year 1000 A.D.⁸ Muslim texts mention the use of cannabis as a diuretic, digestive, anti-flatulent, 'to clean the brain', and to soothe pain of the ears. In 1464, Ibn al-Badri reported that the epileptic son of the caliph's chamberlain was treated with the plant's resin, and stated: it (cannabis) cured him completely, but he became an addict who could not for a moment be without the drug.⁷

Cannabis is known in Africa at least since the 15th century, and its use was, possibly, introduced by Arab traders, somehow connected to India. This is evidenced by the similarity of the terms used for preparing the plant in Africa and India. In Africa, the plant was used for snake bite, to facilitate childbirth, malaria, fever, blood poisoning, anthrax, asthma, and dysentery.⁹

In the Americas, the use of cannabis probably began in South America. In the 16th century, the plant's seeds reached Brazil; brought by African slaves, especially those from Angola, and its use was considerably common among Blacks in the Northeastern rural area. Most synonyms for cannabis in Brazil (maconha, diamba, liamba, and others) have their origin in the Angolan language. There are reports of the use of cannabis in that region's popular religious rituals, especially the 'Catimbó', which includes cult to African deities and presumes the value of the plant for magical practice and treatment of diseases. In the rural environment, there are reports of the use of cannabis for toothache and menstrual cramps.¹⁰

In Europe, during this period, cannabis was cultivated exclusively for fibers. Muslims introduced the manufacture of paper from cannabis, in 1150, first in Spain then in Ita-

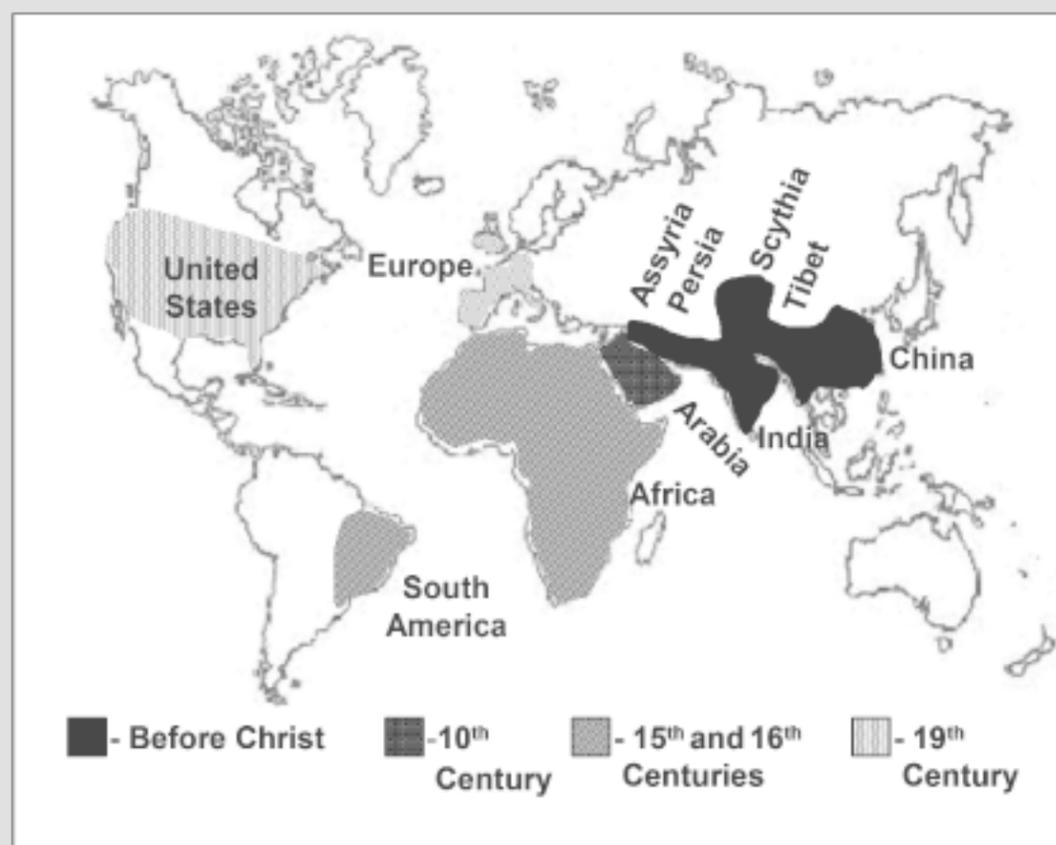
ly.⁷ Cannabis descriptions are found in many books about plants written in this period, which clearly state, since the mid 18th century, the distinction between male and female plants (previously described in a Chinese ideogram in the beginning of the Christian Era).⁷ References to the medical use of cannabis are scarce. Europeans may have known about the plant's medical use in the Middle East and Africa, but they confused it with opium.⁷

Western medicine in the 19th and 20th centuries

There are some reports, from the early 19th century, about the use of cannabis by European physicians, especially regarding the use of the seeds or homeopathic medications. However, the effective introduction of cannabis in Western medicine occurred in the midst 19th century through the works of Willian B. O'Shaughnessy, an Irish physician, and by the book by Jacques-Joseph Moreau, a French psychiatrist.

O'Shaughnessy served in India with the British for several years and made his first contact with cannabis use in that country. He studied the literature on the plant, described many popular preparations, evaluated its toxicity in animals, and, later, he tested its effect on patients with different pathologies. In 1839, he published the work: 'On the preparations of the Indian hemp, or gunjah', which, in the first paragraph, establishes a panorama of plant use:

'The narcotic effects of Hemp are popularly known in the south of Africa, South America, Turkey, Egypt, Middle East Asia, India, and the adjacent territories of the Malays, Burmese, and Siamese. In all these countries, Hemp is used in various forms, by the dissipated and depraved, as the ready agent of a pleasing intoxication. In the popular medicine of these nations, we find it extensively employed for a multitude of affections. But in Western Europe, its use either as a stimulant or as a remedy is equally unknown'⁸



In his book, O'Shaughnessy describes various successful human experiments using cannabis preparations for rheumatism, convulsions, and mainly for muscular spasms of tetanus and rabies.^{6,8}

Moreau used cannabis with a different purpose. He was an assistant physician at the Charenton Asylum, near Paris, and a common therapeutic practice at the time was to accompany psychiatric patients in long trips to exotic and distant countries. During those trips he observed that the use of hashish (cannabis resin) was very common among Arabs, and he was impressed with the substance's surprising effects. In Paris, around 1840, Moreau decided to experiment, systematically, different cannabis preparations; first on himself and later on his students. As an outcome, in 1845 he published the book 'Du Hachisch et de l'Alienation Mentale: Etudes Psychologiques', with one of the most complete descriptions of the acute effects of cannabis.¹¹ Moreau clearly states his purpose: '... I saw in hashish, more specifically in its effects on mental abilities, a powerful and unique method to investigate the genesis of mental illness'.¹²

These two types of medical interest for cannabis, concerning its psychoactive effects (as an experimental psychotomimetic) as well as its therapeutic use, persisted through the years. O'Shaughnessy and Moreau's contributions had a great impact on Western medicine, especially due to the scarcity of therapeutic options for infectious diseases such as rabies, cholera, and tetanus. The medical use of the drug spread from England and France reaching all Europe and then North America. In 1860, the first clinical conference about cannabis took place in America, organized by the Ohio State Medical Society.

In the second half of the 19th century, over 100 scientific articles were published in Europe and the United States about the therapeutic value of cannabis.¹³ The climax of the medical use of cannabis by Western medicine occurred in the late 19th and early

20th century. Various laboratories marketed cannabis extracts or tinctures, such as Merck (Germany), Burroughs-Wellcome (England), Bristol-Meyers Squibb (United States), Parke-Davis (United States), and Eli Lilly (United States).⁸ The medical indications of cannabis, in the beginning of the 20th century, were summarized in Sajous's Analytic Cyclopedia of Practical Medicine (1924) in three areas:⁷

1) Sedative or Hypnotic: in insomnia, senile insomnia, melancholia, mania, delirium tremens, chorea, tetanus, rabies, hay fever, bronchitis, pulmonary tuberculosis, coughs, paralysis agitans, exophthalmic goiter, spasm of the bladder, and gonorrhoea.

2) Analgesic: in headaches, migraine, eye-strain, menopause, brain tumors, tic douloureux, neuralgia, gastric ulcer, gastralgia (indigestion), tabes, multiple neuritis, pain not due to lesions, uterine disturbances, dysmenorrhoea, chronic inflammation, menorrhagia, impending abortion, postpartum hemorrhage, acute rheumatism, eczema, senile pruritus, tingling, formication and numbness of gout, and for relief of dental pain.

3) Other uses: to improve appetite and digestion, for the 'pronounced anorexia following exhausting diseases', gastric neuroses, dyspepsia, diarrhea, dysentery, cholera, nephritis, hematuria, diabetes mellitus, cardiac palpitation, vertigo, sexual atony in the female, and impotence in the male.

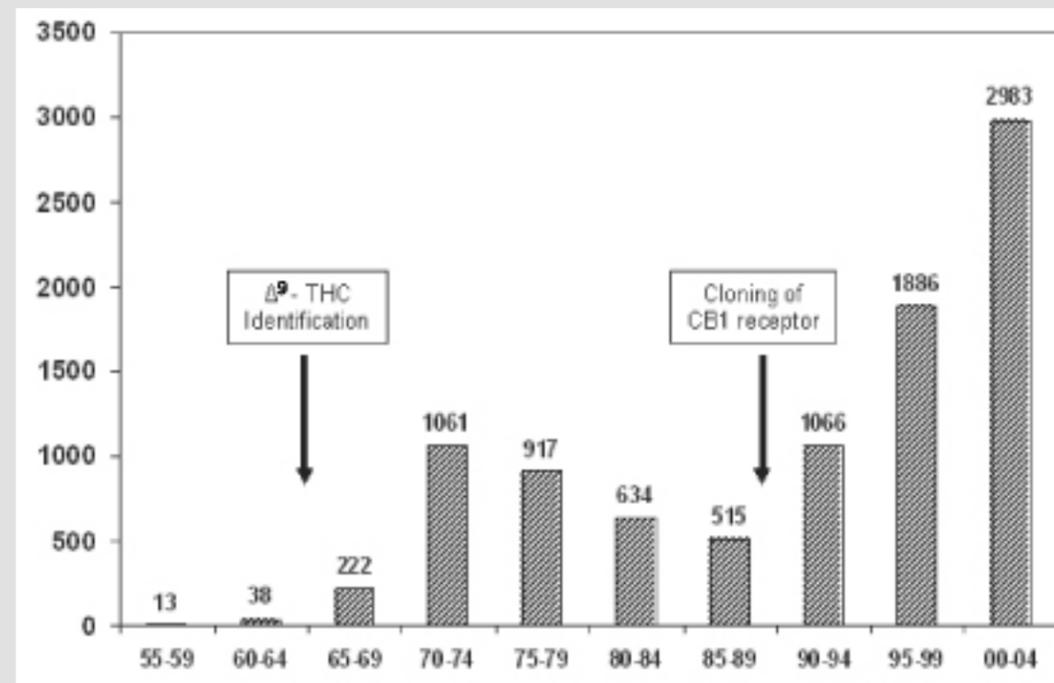


Figure 2 - Number of cannabis-related publications in the last 50 years. The source used was the 'ISI Web Of Knowledge' with the keywords: cannabis or marijuana or marihuana'.

Figure 1 shows an illustration of the periods in which the medical uses of cannabis began in different regions.

Decline and rediscovery

In the first decades of the 20th century, the Western medical use of cannabis significantly decreased. This may have occurred, among other factors, because of the difficulty to obtain replicable effects, due to the extreme varying efficacy of different samples of the

plant. At that time, the active principle of cannabis had not yet been isolated and the drug was used in the form of tinctures or extracts whose power was dependent on different factors, such as origin, age, and mode of preparation.⁸ In addition, various medications appeared at the end of the 19th century, with known efficacy for the treatment of the main indications of cannabis. Vaccines were developed for various infectious diseases, such as tetanus; effective analgesics such as aspirin appeared, and hypodermic syringes allowed the injectable use of morphine; and, as a narcotic and sedative, cannabis was rivaled by substances such as chloral hydrate, paraldehyde, and barbiturates.⁸

Finally, many legal restrictions limited the medical use and experimentation of cannabis. In the United States, as the result of a campaign of the Federal Bureau of Narcotics, the Marihuana Tax Act law was passed in 1937. Under this Act, anyone using the plant was required to register and pay a tax of a dollar an ounce (28.35 g), for medical purposes, and 100 dollars an ounce for any other use. Despite the low value for medical use, the non-payment of this tax, however, resulted in a 2,000 dollar fine and/or 5 years imprisonment. This law brought difficulties for the use of the plant due to the excessive paperwork and the risk of severe punishment. When cannabis transaction regulations, including prescriptions, were transferred to the tribute area, this law circumvented a decision of the Supreme Court which gave the States the right to control commercial transactions and, in practice, meant banning the use of cannabis in the whole American territory. Cannabis was removed from the American pharmacopoeia in 1941.^{6,14}

In the second half of the 20th century, cannabis reached great social importance due to the explosion of its consumption for hedonistic purposes. Until that time, in the West, the hedonistic use of the plant was limited to small groups. In Europe, groups of intellectuals gathered to use the drug. Descriptions of this use may be found in novels by 20th century French writers, such as Gautier and Boudelaire. In the Americas, this practice was relatively common among the Black in the rural area of Northeastern Brazil since the 16th century, who would meet on weekends to use the drug in groups. This use was later passed on to fishermen of the San Francisco River and by sea to the coastal cities. In the early 20th century, the use of cannabis in Brazil remained restricted to small low-socioeconomic groups, and was known as the 'opium of the poor'.¹⁰ In Mexico, cannabis was also used by the most underprivileged population and it was through Mexican immigrants that its use, for recreation, reached the United States in the first decades of

the 20th century. Until the 1950's, in the United States, cannabis use was restricted to the neighborhoods of Blacks and Hispanic immigrants.¹⁵

Since the 1960's, the recreational use of cannabis rapidly spread among the younger ranges of the population throughout the Western world. In the United States, the percentage of young adults that had used cannabis, at least once, went from 5%, in 1967, to 44%, 49%, 68%, and 64%, in 1971, 1975, 1980, and 1982, respectively.¹⁶⁻¹⁷ This use remains high until today.¹⁸⁻¹⁹ In 1964, the chemical structure of D9-THC was identified by Gaoni and Mechoulam,²⁰ which contributed to a proliferation of studies about the active constituents of cannabis.²¹

The startling boost in cannabis consumption, which intensified its social importance, along with the better knowledge of its chemical composition (which made it possible to obtain its pure constituents) contributed to a significant increase in scientific interest for cannabis, as of 1965. The number of publications about cannabis reached their peak in the early 1970's. In this period, a Brazilian research group, led by Carlini, had a great contribution, especially about the interactions of D9-THC with other cannabinoids.²² Since then, Carlini has been developing efforts for the realignment of public policies concerning cannabis control.²³ After the middle of 1970's, the number of publications started to slowly decline during the following two decades. The interest in studies about cannabis was renewed in the early 1990's, with the description and cloning of specific receptors for the cannabinoids in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.²⁴ Afterwards, the number of publications about cannabis has been continuously growing, attesting the great interest in research involving the herb. Figure 2 shows the evolution of the number of publications about cannabis in the last 50 years.

With the growth of scientific interest for cannabis, its therapeutic effects are being once again studied, this time using more accurate scientific methods. There are studies, in different phases, about the therapeutic effects of D9-THC in conditions such as: epilepsy, insomnia, vomits, spasms, pain, glaucoma, asthma, inappetence, Tourette syndrome, and others. Among the therapeutic indications of D9-THC the following are considered close to being proven: anti-emetic, stimulant of appetite, analgesic, and in symptoms of Multiple Sclerosis.²⁵ Other cannabinoids are also under investigation, such as Cana-

bidiol (CBD), which has evidence for therapeutic effects in epilepsy, insomnia, anxiety, inflammations, brain damage (as a neuroprotector), psychoses, and others.²⁶⁻²⁷ However, cannabis products must be used cautiously since some studies suggest that early-onset cannabis use can induce cognitive deficits and apparently acts as a risk factor for the onset of psychosis among vulnerable youths.²⁸⁻²⁹

At the beginning of 2005, a multinational pharmaceutical laboratory received the approval in Canada, and is pleading authorization in the United Kingdom and the European Union, to market a medication containing D9-THC and CBD for the relief of neuropathic pain in patients with multiple sclerosis.

Thus, a new cycle begins for the use of cannabis derivatives as medication, this time more consistently than in the past. The structures of chemical compounds derived from cannabis are now known, the mechanisms of their action in the nervous system are being elucidated with the discovery of an endogenous cannabinoid system, and treatment effectiveness and safety are being scientifically proven.

Acknowledgements

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Pulmonary consequences of marijuana smoking

Pfeifer AK1, Lange P.

1. H:S Hvidovre Hospital, Hjerte-Lungemedicinsk Afdeling, Hvidovre

<http://www.ncbi.nlm.nih.gov/pubmed/16729923>

Based on previously published studies, this review describes the pulmonary consequences of marijuana smoking. Smoking of marijuana is significantly associated with chronic bronchitis (cough and phlegm), but it has not been firmly established whether it also leads to a reduction in lung function. Both epidemiological studies and case reports suggest that regular smokers of marijuana have a higher risk of developing malignancies in both the upper and lower airways. Smoking of marijuana contaminated with fungus spores has been reported to lead to pulmonary aspergillus infections in immunocompromised patients, and sharing of marijuana water pipes has been associated with transmission of tuberculosis.

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Cannabinoids in medicine: A review of their therapeutic potential

By M. Ben Amar

Substance Abuse Program, Faculties of Continuing Education and Graduate Studies, University of Montreal, C.P. 6128, succursale Centre-ville, Montreal, Que. H3C 3J7, Canada
mohamed.ben.amar@umontreal.ca

<http://www.ncbi.nlm.nih.gov/pubmed/16540272>

In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded. Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

Targeting the endocannabinoid system in treating brain disorders

Bahr BA1, Karanian DA, Makanji SS, Makriyannis A.

1. Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT 06269, USA
Bahr@uconn.edu

<http://www.ncbi.nlm.nih.gov/pubmed/16548785>

Recent cannabinoid research has a primary focus on developing therapeutics against human diseases. Many studies on cannabinoids indicate important progress for protection against several neurodegenerative disorders. Agonists of cannabinoid receptors activate signalling pathways in the brain that are linked to neuronal repair and cell maintenance, and endogenous ligands can also activate neuroprotective responses. These endocannabinoids are bioactive fatty acid amides and esters that are synthesised in the brain and include arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol. Endocannabinoids are released in response to pathogenic events, thus representing a potential compensatory repair mechanism. Enhancing this on-demand action of endocannabinoids is a strategy with which to promote endogenous repair signalling. For such enhancement, considerable work has gone into modulating the availability of endocannabinoids by blocking the processes of their deactivation. The targets include the anandamide-hydrolysing enzyme fatty acid amide hydrolase, the carrier-mediated anandamide transport system and 2-arachidonoyl glycerol-deactivating enzyme monoacylglycerol lipase. The activity of endocannabinoids is terminated through transport and degradation and, accordingly, selective inhibitors of these processes effectively exploit the protective nature of cannabinergic responses. This review highlights recent studies implicating the endocannabinoid system in neuroprotection against different disorders of the CNS.

Expert Opinions In Pharmacotherapy • April 2006

Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain

By M.P. Barnes

Hunters Moor Regional Neurological Rehabilitation Centre, Newcastle upon Tyne, NE2 4NR, UK
m.p.barnes@btinternet.com

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Sativex is one of the first cannabis-based medicines to undergo conventional clinical development and to be approved as a prescription medicine. It is an oromucosal spray that allows flexible, individualised dosing. Patients self titrate their overall dose and pattern of dosing according to their response to and tolerance of the medicine. This usually results in the administration of approximately 8-12 sprays/day. Each spray delivers tetrahydrocannabinol 2.7 mg and cannabidiol 2.5 mg, giving an approximate average dose of tetrahydrocannabinol 22-32 mg/day and cannabidiol 20-30 mg/day. Development has concentrated on the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain, as well as the treatment of neuropathic pain of other aetiologies. Positive results in placebo-controlled trials of the use of Sativex as an add-on therapy in these indications demonstrate that Sativex is efficacious and well tolerated in the treatment of these symptoms. Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada. If ongoing studies replicate the results already observed, further approvals for the treatment of spasticity in multiple sclerosis and for neuropathic pain are likely.

The pharmacology of cannabinoid receptors and their ligands: an overview

By R.G. Pertwee

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK
rgp@abdn.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/19559360>

Mammalian tissues express at least two cannabinoid receptor types, CB1 and CB2, both G protein coupled. CB1 receptors are found predominantly at nerve terminals where they mediate inhibition of transmitter release. CB2 receptors occur mainly on immune cells, one of their roles being to modulate cytokine release. Endogenous agonists for cannabinoid receptors also exist, and are all eicosanoids. The first-discovered of these 'endocannabinoids' was arachidonylethanolamide and there is convincing evidence that this ligand and some of its metabolites can activate vanilloid VRI (TRPV1) receptors. Certain cannabinoids also appear to have TRPV1-like and/or non-CB1, non-CB2, non-TRPV1 targets. Several CB1- and CB2-selective agonists and antagonists have been developed. Antagonists include the CB1-selective SR141716A, AM251, AM281 and LY320135, and the CB2-selective SR144528 and AM630. These all behave as inverse agonists, one indication that CB1 and CB2 receptors can exist in a constitutively active state. 'Neutral' cannabinoid receptor antagonists have also been developed. CB1 and/or CB2 receptor activation appears to ameliorate inflammatory and neuropathic pain and certain multiple sclerosis symptoms. This might be exploited clinically by using CB1, CB2 or CB1/CB2 agonists, or inhibitors of the membrane transport or catabolism of endocannabinoids that are released in increased amounts, at least in animal models of pain and multiple sclerosis. We have recently discovered the presence of an allosteric site on the CB1 receptor. Consequently, it may also prove possible to enhance 'autoprotective' effects of released endocannabinoids with CB1 allosteric enhancers or, indeed, to reduce proposed 'autoimpairing' effects of released endocannabinoids such as excessive food intake with CB1 allosteric antagonists.

Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug

Zuardi AW1, Crippa JA, Hallak JE, Moreira FA, Guimarães FS.

1. Departamento de Neurologia, Psiquiatria e Psicologia Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
awzuardi@fmrp.usp.br

Full text, PDF, with 50 references

<http://www.scielo.br/pdf/bjmbr/v39n4/6164.pdf>

A high dose of delta9-tetrahydrocannabinol, the main Cannabis sativa (cannabis) component, induces anxiety and psychotic-like symptoms in healthy volunteers. These effects of delta9-tetrahydrocannabinol are significantly reduced by cannabidiol (CBD), a cannabis constituent which is devoid of the typical effects of the plant. This observation led us to suspect that CBD could have anxiolytic and/or antipsychotic actions. Studies in animal models and in healthy volunteers clearly suggest an anxiolytic-like effect of CBD. The antipsychotic-like properties of CBD have been investigated in animal models using behavioral and neurochemical techniques which suggested that CBD has a pharmacological profile similar to that of atypical antipsychotic drugs. The results of two studies on healthy volunteers using perception of binocular depth inversion and ketamine-induced psychotic symptoms supported the proposal of the antipsychotic-like properties of CBD. In addition, open case reports of schizophrenic patients treated with CBD and a preliminary report of a controlled clinical trial comparing CBD with an atypical antipsychotic drug have confirmed that this cannabinoid can be a safe and well-tolerated alternative treatment for schizophrenia. Future studies of CBD in other psychotic conditions such as bipolar disorder and comparative studies of its antipsychotic effects with those produced by clozapine in schizophrenic patients are clearly indicated.

The endogenous cardiac cannabinoid system: a new protective mechanism against myocardial ischemia

Lamontagne D1, Lépicier P, Lagneux C, Bouchard JF.

1. Faculté de pharmacie, Université de Montréal, QC, Canada
daniel.lamontagne@umontreal.ca

<http://www.ncbi.nlm.nih.gov/pubmed/16618028>

The pharmacological (and recreational) effects of cannabis have been known for centuries. However, it is only recently that one has identified two subtypes of G-protein-coupled receptors, namely CB1 and CB2-receptors, which mediate the numerous effects of delta9-tetrahydrocannabinol and other cannabinoids. Logically, the existence of cannabinoid-receptors implies that endogenous ligands for these receptors (endocannabinoids) exist and exert a physiological role. Hence, arachidonylethanolamide (anandamide) and sn-2 arachidonoylglycerol, the first two endocannabinoids identified, are formed from plasma membrane phospholipids and act as CB1 and/or CB2 agonists. The presence of both CB1 and CB2-receptors in the rat heart is noteworthy. This endogenous cardiac cannabinoid system is involved in several phenomena associated with cardioprotective effects. The reduction in infarct size following myocardial ischemia, observed in rats exposed to either LPS or heat stress 24 hours before, is abolished in the presence of a CB2-receptor antagonist. Endocannabinoids and synthetic cannabinoids, the latter through either CB1 or CB2-receptors, exert direct cardioprotective effects in rat isolated hearts. The ability of cannabinoids to reduce infarct size has been confirmed in vivo in anesthetized mice and rats. This latter effect appears to be mediated through CB2-receptors. Thus, the endogenous cardiac cannabinoid system, through activation of CB2-receptors, appears to be an important mechanism of protection against myocardial ischemia.

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Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults

Smith AM1, Fried PA, Hogan MJ, Cameron I.

1. Department of Psychology, University of Ottawa, Ottawa, Ontario, Canada
asmith@uottawa.ca

<http://www.ncbi.nlm.nih.gov/pubmed/16473495>

The long lasting neurophysiological effects of prenatal marijuana exposure on visuospatial working memory were investigated in 18-22 year olds using functional magnetic resonance imaging (fMRI). The participants are members of the Ottawa Prenatal Prospective Study (OPPS), a longitudinal study that provides a unique body of information collected from each participant over 20 years, including prenatal drug history, detailed cognitive/behavioral performance from infancy to young adulthood, and current and past drug usage. This information allowed for the control of potentially confounding drug exposure variables in the statistical analyses. Thirty-one offspring from the OPPS (16 prenatally exposed and 15 nonexposed) performed a visuospatial 2-back task while neural activity was imaged with fMRI. Cognitive performance data were also collected. No significant performance differences were observed when comparing controls versus exposed participants. Multiple regression analyses (including controls with no exposure) revealed that as the amount of prenatal marijuana exposure increased, there was significantly more neural activity in the left inferior and middle frontal gyri, left parahippocampal gyrus, left middle occipital gyrus and left cerebellum. There was also significantly less activity in right inferior and middle frontal gyri. These results suggest that prenatal marijuana exposure alters neural functioning during visuospatial working memory processing in young adulthood.

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Cannabis use and the mental health of young people

By W.D. Hall

University of Queensland, Herston, Australia
w.hall@sph.uq.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/16476127>

This paper critically reviews epidemiological evidence on the following psychosocial consequences of adolescent cannabis use: cannabis dependence; the use of heroin and cocaine; educational underachievement; and psychosis. Leading electronic databases such as PubMed have been searched to identify large-scale longitudinal studies of representative samples of adolescents and young adults conducted in developed societies over the past 20 years.

Cannabis is a drug of dependence, the risk of which increases with decreasing age of initiation. Cannabis dependence in young people predicts increased risks of using other illicit drugs, underperforming in school, and reporting psychotic symptoms. Uncertainty remains about which of these relationships are causal although the evidence is growing that cannabis is a contributory cause of psychotic symptoms.

We face major challenges in communicating with young people about the most probable risks of cannabis use (dependence, educational underachievement and psychosis) given uncertainties about these risks and polarized community views about the policies that should be adopted to reduce them.

Pain and politics: DEA, Congress, and the courts, Oh My!

By S.M. Fishman

Division of Pain Medicine, University of California, Davis, CA, USA

<http://painmedicine.oxfordjournals.org/content/7/1/87.long>

In this issue, Howard Heit describes a pressing problem that faces two public health crises that are seemingly at odds with each other. Although few would question that combating drug abuse as well as resolving the under treatment of pain justify our attention and resources, helping one need not harm the other. The perfect storm in which these issues are now colliding stems from real public needs and agencies and professionals who are focused, perhaps too narrowly, on each of their individual causes. There are no real bad guys here even though some in law enforcement may see some well-intended physicians as drug dealers and some from the pain community may see the Drug Enforcement Administration (DEA) leadership as disingenuous and lacking in respect or concern for the collateral victims of their antidrug abuse activities. The reality here is that healthcare workers focus on improving health and, in large part, are not primarily invested in the enforcement of laws to prevent drug abuse. Law enforcement is just the opposite, with primary responsibility in fighting abuse as set forth by the law, with friendly fire being the price of doing business. No wonder we hear the DEA present themselves in the best public light, as the same old physician-friendly agency, while almost simultaneously, their behavior suggests a diametrically different position. It is as though their words and their music go with two different songs.

In light of several other governmental initiatives that have challenged the line between health policy and law enforcement, the current state of affairs with the DEA is just one of several examples of a subtle shift in governmental oversight of medicine from agencies responsible for public health to law enforcement. For instance, just last year, Congress gave the DEA increased authority for reviewing new drugs, a role that has always been held solely with the Food and Drug Ad-

ministration (FDA). The new authority came through an almost secret process as it was not legislated through the normal process of making law, but legislated directly through appropriation of funding to the DEA, a process known as legislation through appropriation. This process occurred with no public review or commentary. The new authority was vague and exactly how it could impact patients is not clear. It is clear however, that a real line was crossed as prior to this new law, approving new drugs was the sole function of the government agency that focused on health and drugs, the FDA. Through this legislative shell game, the FDA's oversight for new medicines became shared with a government agency that is solely focused on drug abuse (DEA). Law enforcement and healthcare policy have often been intentionally separated so that one does not interfere with the other. In light of the detrimental effects that this change could have on the development of new analgesics, members of the pain care community raised concerns, attracted media attention, and recruited political support. On November 4, 2005, Congress reversed itself and removed the new authority as well as the 50 million dollars it had granted to the DEA just 1 year earlier. Nonetheless, the message here was clear, that many in positions of power believe that policies to decrease drug abuse take precedent over other public health concerns.

The potential role of the DEA in FDA activities is just one example of a disturbing trend of regulatory authority over healthcare shifting away from health agencies and to law enforcement agencies. The DEA and federal prosecutors have increased scrutiny of physicians' practices by using the courts to bypass state medical boards to bring criminal charges against doctors. Although the practice of Dr. William Hurwitz was arguably at an extreme or even beneath the standard

of care, review of the court proceeding of his prosecution for drug trafficking reflects a breach of an important separation between medicine and criminal activity. This line has traditionally protected society from the potential of law enforcement to degrade the quality of the public's health care—in essence, the effect of paralyzing legitimate clinicians who would otherwise be fearful of wrongful prosecution. In the federal trial of Dr. Hurwitz, the jury was never given adequate instructions on the difference between an individual prescribing abusable substances within the bounds of medicine and those dealing drugs outside these bounds. Hurwitz was convicted on 50 counts (and sentenced to 25 years in federal prison) by a jury who was given woefully inadequate guidance on the law that specifically seeks to protect physicians, even those who practice substandard medicine, from criminal prosecution when they are acting in good faith. Whether Hurwitz was or was not acting in good faith as a treating physician was therefore not even allowed to be a consideration for this jury. The precedent set in this case has dire implications for any legitimate physician who may need to appropriately treat a patient with aggressive dosages of a potentially abusable medication. If this is drug trafficking, who among the legions of physicians who treat pain every day are not drug traffickers? At the time of this writing, the 4th District Court of Appeals is poised to hear these arguments. Nonetheless, in its service to adjudicate and enforce the law, the willingness of the original federal court to potentially change the practice of medicine through this precedent setting action again reflects the zeal to combat drug abuse, even at the expense of public health.

Another example of shifting oversight of medicine in general and pain care in particular, is the recently passed law instituting a national prescription monitor program called the National All Schedules Prescription Electronic Reporting Act (NASPER.) This new program is specifically intended to encourage states to develop their own prescription monitoring programs (PMPs) for schedule II and other abusable drugs. PMPs have become a necessary part of pharmacovigilance at a time when prescription drug abuse is alarmingly on the rise. However, while it is well known that such PMPs can be used as helpful tools for enhancing safe prescribing, when administered with the appearance of law enforcement, they can impede optimal prescribing and even perpetuate aberrant prescribing that may facilitate abuse. Unfortunately, NASPER is suspiciously vague, leaving it up to each state to decide whether they will even participate. Moreover, the law neither mandates that the authority to monitor prescribing would come under state agencies

responsible for health rather than law enforcement, nor does it ensure that the collected information would be available to physicians at the time that they treat their patients. These profound inadequacies suggest that this law may be intended less as a clinical tool than as a physician mouse trap.

Drug abuse and under treated pain are both public health crises, but there is no evidence to suggest that the solution to one must impact the other. In fact, new evidence by Joransen et al. [1] suggests that the growing problem of prescription drug abuse may be much less related to prescribers than to theft of the drugs at points along the supply chain that do not include clinicians (REF). Therefore, targeting physicians may make good press for government agencies that have little good news to report on the war on drugs, but these efforts are unlikely to significantly curb drug abuse in America.

The regulation of medicine has traditionally been held with government agencies responsible for health and not law enforcement because this separation offers the greatest public benefit and least risk of incidental harm. The scenario described in the preceding essay by Heit of the DEA intruding into the practice of medicine by reinterpreting the Controlled Substances Act has its own incidental harm that may ironically reduce safe prescribing and increase abuse risk. But this incidental harm is not the primary concern of the DEA. Neither is it the concern of courts that zealously criminalize physicians who practice within the bounds of medicine nor politically minded legislators that pass laws with the appearance of strong antidrug programs.

Healthcare decisions, including those involving legitimate use of analgesics, must remain in the hands of healthcare professionals. The DEA should be required to work with health agencies and healthcare professionals in finding common ground and reaching the rational position of balance that is in the public's best interest. Fortunately, Congress, who ultimately gives the DEA its funding, may be seeing the writing on the wall. Healthcare oversight must remain within agencies whose primary responsibility is to improve public health. Contrary to recent events in Washington, we must continue to insist that drug abuse can be curbed without undermining patients in pain and striving for such policies is in the best interest of society. The least we can do is to make sure that the casualties of the war on drugs are not suffering patients who legitimately deserve relief.

Pain, the DEA, and the impact on patients

By W. Rowe

American Pain Foundation, Baltimore, MD, USA.

Full text

<http://painmedicine.oxfordjournals.org/content/7/1/86>

Dr. Heit provides an excellent summary of the events that constitute the history of the attempt to create balance—curbing diversion while simultaneously protecting access to pain medicines. It is, unfortunately, a sad story. Going from the optimism after producing and disseminating Prescription Pain Medications: Frequently Asked Questions and Answers (FAQ), to the disappointment of the abrupt withdrawal of the same document with subsequent “clarifications” that reflected a significant retreat from the goal of protecting access to pain medicines for people who need them, the story’s current ending has many, many victims—people affected by pain.

From the perspective of the pain patient, things have gotten worse. It is harder to get prescriptions for Schedule II pain medicines because prescribers are even more reluctant to prescribe. They are reluctant because they are not clear what is acceptable and what is not acceptable, and it is safer to avoid any opportunity for confusion. Also, things are worse because the long understood method of writing prescriptions had been changed by not allowing a prescriber to prepare multiple prescriptions on the same day with instructions to fill on different dates. Dr. Heit concludes that “the spirit of cooperation that existed between the DEA and the pain community to achieve the goal of balance has broken down.”

The rise of the abuse and diversion of prescription medicines has precipitated a loud demand from the President on down to stop the abuse of pre-

scription medicines. This command, siloed as it is in the Department of Justice, is seriously flawed. It is flawed the same way that it is wrong to curb the rise of parking problems by banning the use of cars on weekends. You are guaranteed to have fewer parking problems, but you will have prohibited access to cars to a great number of people who need and deserve the use of their cars. The correct command should read: stop the abuse and diversion of prescription medicines without harming access to these medicines for people affected by pain. That command is not directing the activities of the Drug Enforcement Administration (DEA). If it were they would not be arresting doctors at the rate occurring today around the country; they would not have withdrawn the FAQ; they would not agree to be in a veto position to newly approved Food and Drug Administration medicines; they would not have virtually withdrawn from the dialogue about achieving balance.

The failure here is in the DEA not abiding by its commitment to the pain community to pursue balance. It is also the failure of those in authority over the DEA to assert the more comprehensive command. This is not a simple law enforcement issue. The needs and rights of millions of pain patients are neglected in the abbreviated command. To those who authorize the DEA, surely if it was your mother, partner, or friends who could not get the medicine they need because of the practice of law enforcement, you would insist that law enforcement measures not trample the needs and rights of those requiring these medicines to live normal lives.

DEA and pain practitioners: common goals, adversarial stance?

By E. Covington

Chronic Pain Rehabilitation Program, Cleveland Clinic Foundation, Cleveland, OH, USA

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Dr. Heit has well articulated the conundrum in which those of us who treat pain find ourselves, and the path that led to the present situation. While there are several points of minor disagreement, the major problems are two—the change involving the “do not fill until” rule and the change in attitude.

Part of our difficulty is inescapable. Most medical decisions affect only patients, and therefore judgments are an issue between practitioner and patient. In the case of controlled substances (CS), however, our prescriptions have a demonstrable impact on the larger society. Given even a weak relationship between prescriptions for a substance and negative impacts on society, every prescription, no matter how appropriate, has the effect of increasing the quantity available to be stolen from pharmacies and medicine cabinets, in addition to the risks to the person for whom it is prescribed. Therefore, we cannot escape the often frustrating tail-wags-the-dog scenario of feeling told how to treat our patients by people who may know little of the science and none of the issues of the individual patient. Nor can we escape the conflict between our obligation to meet patient needs for analgesia and our desire to minimize the drugs available at teenage parties.

We are not alone in having conflicting goals. The Drug Enforcement Administration (DEA) has mandates both to ensure lawful access and to restrict unlawful access. Pursuit of either goal will, of necessity, have the potential to adversely affect the other. Our mutual challenges were helped remarkably by the efforts of the DEA in recent years to establish a collaborative relationship with the pain treatment community. The resulting dialog was

clearly beneficial to all. The abrupt, unilateral withdrawal of Prescription Pain Medications: Frequently Asked Questions and Answers (FAQ) felt to the pain community like a betrayal. Absent a clear explanation, we are left to speculate whether the DEA was insincere, succumbed to political pressure, or had a sudden epiphany regarding the “correct” understanding of the legislation that was not apparent previously to the DEA or subsequently to physicians in the pain community.

Dr. Heit enumerated several benefits of “Do Not Fill Until” (DNF) prescriptions and several hazards of the alternative strategies for providing chronic opioid therapy. I have heard no downsides to the DNF practice, other than the DEA’s allegation that dishonest doctors do it. Perhaps, pain practitioners are not seeing problems with DNF because most of us insist on patient permission to communicate freely with their dispensing pharmacists—a strategy that could be encouraged by the DEA.

Potential difficulties, clearly, could have been productively addressed by continued collaboration. They have instead been exacerbated by the unilateral and ill-advised interim policy statement. Just as legitimate prescriptions pose some risk to society, so too do legitimate restrictions pose a risk that the hassle and fear factors of treating pain patients will dissuade good doctors from doing so. It seems essential that collaboration resume. The only alternative would be legislative remedies, which have the potential to be even less scientifically based and more disruptive to appropriate practice, with the consequences to be borne by those already burdened with chronic pain.

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Transitional cell carcinoma associated with marijuana: case report and review of the literature

Nieder AM1, Lipke MC, Madjar S.

Department of Urology, State University of New York, Stony Brook, New York, USA
anieder1@med.miami.edu

<http://www.ncbi.nlm.nih.gov/pubmed/16413373>

Transitional cell carcinoma of the bladder tends to occur in older patients with a history of tobacco use. We recently evaluated and treated a 45-year-old man with a history of heavy marijuana use. The patient's only risk factor for transitional cell carcinoma was the inhalation of up to five marijuana cigarettes daily for more than 30 years. We present our case and review the literature.

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Association between marijuana use and transitional cell carcinoma

Chacko JA1, Heiner JG, Siu W, Macy M, Terris MK.

Department of Urology, Stanford University Medical Center, Stanford, California, USA

<http://www.ncbi.nlm.nih.gov/pubmed/16413342>

Marijuana smoking has been implicated as a causative factor in traditionally tobacco-related tumors of the head and neck and of the lung. When associated with marijuana use, such tumors occur in a much younger patient population than do similar tumors in tobacco smokers. Owing to the large number of young men with a history of marijuana presenting with transitional cell carcinoma to VA facilities, this study was designed to compare the marijuana use among young (aged less than 60 years) transitional cell carcinoma patients with that among age-matched controls. Fifty-two men aged less than 60 years presenting consecutively with transitional cell carcinoma and 104 age-matched controls (defined by having no history of transitional cell carcinoma, hematuria, or irritative voiding symptoms, as well as unremarkable results on urinalysis and urine cytology) completed questionnaires about exposure to various potential carcinogens, including radiation, Agent Orange, smoked or processed meats, dyes, tobacco, and marijuana. Of the 52 transitional cell carcinoma patients, 46 (88.5%) reported a history of habitual marijuana usage, and 72 (69.2%) of the age-matched controls gave a history of habitual marijuana use. This difference was statistically significant ($P = 0.008$). In those with transitional cell carcinoma, marijuana use significantly correlated with tumor stage, grade, and number of recurrences.

Marijuana smoking might increase the risk of transitional cell carcinoma.

From cannabis to endocannabinoids in multiple sclerosis: a paradigm of central nervous system autoimmune diseases

Malfitano AM1, Matarese G, Bifulco M.

Dipartimento di Scienze Farmaceutiche, Universita' di Salerno, Fisciano (Sa), Italy

<http://www.ncbi.nlm.nih.gov/pubmed/16375684>

An increasing body of evidence suggests that cannabinoids have beneficial effects on the symptoms of multiple sclerosis, including spasticity and pain. Endogenous molecules with cannabinoid-like activity, such as the "endocannabinoids", have been shown to mimic the anti-inflammatory properties of cannabinoids through the cannabinoid receptors. Several studies suggest that cannabinoids and endocannabinoids may have a key role in the pathogenesis and therapy of multiple sclerosis. Indeed, they can down regulate the production of pathogenic T helper 1-associated cytokines enhancing the production of T helper 2-associated protective cytokines. A shift towards T helper 2 has been associated with therapeutic benefit in multiple sclerosis. In addition, cannabinoids exert a neuromodulatory effect on neurotransmitters and hormones involved in the neurodegenerative phase of the disease. In vivo studies using mice with experimental allergic encephalomyelitis, an animal model of multiple sclerosis, suggest that the increase of the circulating levels of endocannabinoids might have a therapeutic effect, and that agonists of endocannabinoids with low psychoactive effects could open new strategies for the treatment of multiple sclerosis.

Cannabinoid function in learning, memory and plasticity

Riedel G1, Davies SN.

School of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK
g.riedel@abdn.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/16596784>

Marijuana and its psychoactive constituents induce a multitude of effects on brain function. These include deficits in memory formation, but care needs to be exercised since many human studies are flawed by multiple drug abuse, small sample sizes, sample selection and sensitivity of psychological tests for subtle differences. The most robust finding with respect to memory is a deficit in working and short-term memory. This requires intact hippocampus and prefrontal cortex, two brain regions richly expressing CB1 receptors. Animal studies, which enable a more controlled drug regime and more constant behavioural testing, have confirmed human results and suggest, with respect to hippocampus, that exogenous cannabinoid treatment selectively affects encoding processes. This may be different in other brain areas, for instance the amygdala, where a predominant involvement in memory consolidation and forgetting has been firmly established. While cannabinoid receptor agonists impair memory formation, antagonists reverse these deficits or act as memory enhancers. These results are in good agreement with data obtained from electrophysiological recordings, which reveal reduction in neural plasticity following cannabinoid treatment, and increased plasticity following antagonist exposure. The mixed receptor properties of the pharmacological tool, however, make it difficult to define the exact role of any CB1 receptor population in memory processes with any certainty. This makes it all the more important that behavioural studies use selective administration of drugs to specific brain areas, rather than global administration to whole animals. The emerging role of the endogenous cannabinoid system in the hippocampus may be to facilitate the induction of long-term potentiation/the encoding of information. Administration of exogenous selective CB1 agonists may therefore disrupt hippocampus-dependent learning and memory by 'increasing the noise', rather than 'decreasing the signal' at potentiated inputs.

Cannabinoids

By F. Grotenhermen

Nova-Institut, Goldenbergstrasse 2, D-50354 Hürth, Germany
franjo.grotenhermen@nova-institut.de

<http://www.ncbi.nlm.nih.gov/pubmed/16266285>

Since the discovery of an endogenous cannabinoid system, research into the pharmacology and therapeutic potential of cannabinoids has steadily increased. Two subtypes of G-protein coupled cannabinoid receptors, CB₁ and CB₂, have been cloned and several putative endogenous ligands (endocannabinoids) have been detected during the past 15 years. The main endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), derivatives of arachidonic acid, that are produced "on demand" by cleavage of membrane lipid precursors. Besides phytocannabinoids of the cannabis plant, modulators of the cannabinoid system comprise synthetic agonists and antagonists at the CB receptors and inhibitors of endocannabinoid degradation. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues, including immune system, reproductive and gastrointestinal tracts, sympathetic ganglia, endocrine glands, arteries, lung and heart. There is evidence for some non-receptor dependent mechanisms of cannabinoids and for endocannabinoid effects mediated by vanilloid receptors. Properties of CB receptor agonists that are of therapeutic interest include analgesia, muscle relaxation, immunosuppression, anti-inflammation, antiallergic effects, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects. The current main focus of clinical research is their efficacy in chronic pain and neurological disorders. CB receptor antagonists are under investigation for medical use in obesity and nicotine addiction. Additional potential was proposed for the treatment of alcohol and heroine dependency, schizophrenia, conditions with lowered blood pressure, Parkinson's disease and memory impairment in Alzheimer's disease.

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Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis

Rog DJ1, Nurmikko TJ, Friede T, Young CA.

Walton Centre for Neurology and Neurosurgery, University of Liverpool, Liverpool, UK
djrdjr@doctors.org.uk

<http://www.ncbi.nlm.nih.gov/pubmed/16186518>

Central pain in multiple sclerosis (MS) is common and often refractory to treatment. Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated.

Sativex for the management of multiple sclerosis symptoms

By C. Perras

<http://www.ncbi.nlm.nih.gov/pubmed/16317825>

Sativex (R) is a cannabis-based pharmaceutical product containing delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, delivered in an oromucosal (mouth) spray. It has been approved as adjunctive treatment for neuropathic pain in patients with multiple sclerosis (MS). It is being investigated for the management of other MS symptoms, such as spasticity. THC:CBD spray is regulated as a narcotic. Five randomized controlled trials (RCTs) compared the benefits and harms of THC:CBD spray with placebo. A total of 368 patients with various neurological conditions (including MS) were recruited. In some trials, THC:CBD spray significantly reduced neuropathic pain, spasticity, muscle spasms and sleep disturbances. The most common adverse events (AEs) reported in trials were dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste. Long-term safety and the potential for dependence, abuse, misuse and diversion are unknown.

Pharmacokinetics and metabolism of the plant cannabinoids, delta9-tetrahydrocannabinol, cannabidiol and cannabinol.

By M.A. Huestis

Chemistry and Drug Metabolism, Intramural Research Program, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA
mhuestis@intra.nida.nih.gov

<http://www.ncbi.nlm.nih.gov/pubmed/16596792>

Increasing interest in the biology, chemistry, pharmacology, and toxicology of cannabinoids and in the development of cannabinoid medications necessitates an understanding of cannabinoid pharmacokinetics and disposition into biological fluids and tissues. A drug's pharmacokinetics determines the onset, magnitude, and duration of its pharmacodynamic effects. This review of cannabinoid pharmacokinetics encompasses absorption following diverse routes of administration and from different drug formulations, distribution of analytes throughout the body, metabolism by different tissues and organs, elimination from the body in the feces, urine, sweat, oral fluid, and hair, and how these processes change over time. Cannabinoid pharmacokinetic research has been especially challenging due to low analyte concentrations, rapid and extensive metabolism, and physicochemical characteristics that hinder the separation of drugs of interest from biological matrices--and from each other--and lower drug recovery due to adsorption of compounds of interest to multiple surfaces. delta9-Tetrahydrocannabinol, the primary psychoactive component of *Cannabis sativa*, and its metabolites 11-hydroxy-delta9-tetrahydrocannabinol and 11-nor-9-carboxy-tetrahydrocannabinol are the focus of this chapter, although cannabidiol and cannabinol, two other cannabinoids with an interesting array of activities, will also be reviewed. Additional material will be presented on the interpretation of cannabinoid concentrations in human biological tissues and fluids following controlled drug administration.

Human studies of cannabinoids and medicinal cannabis

By P. Robson

Department of Psychiatry, Oxford University, Warneford Hospital, Oxford OX3 7JX, UK
pjr@gwpharm.com

<http://www.ncbi.nlm.nih.gov/pubmed/16596794>

Cannabis has been known as a medicine for several thousand years across many cultures. It reached a position of prominence within Western medicine in the nineteenth century but became mired in disrepute and legal controls early in the twentieth century. Despite unremitting world-wide suppression, recreational cannabis exploded into popular culture in the 1960s and has remained easily obtainable on the black market in most countries ever since. This ready availability has allowed many thousands of patients to rediscover the apparent power of the drug to alleviate symptoms of some of the most cruel and refractory diseases known to humankind. Pioneering clinical research in the last quarter of the twentieth century has given some support to these anecdotal reports, but the methodological challenges to human research involving a pariah drug are formidable. Studies have tended to be small, imperfectly controlled, and have often incorporated unsatisfactory synthetic cannabinoid analogues or smoked herbal material of uncertain composition and irregular bioavailability. As a result, the scientific evaluation of medicinal cannabis in humans is still in its infancy. New possibilities in human research have been opened up by the discovery of the endocannabinoid system, a rapidly expanding knowledge of cannabinoid pharmacology, and a more sympathetic political environment in several countries. More and more scientists and clinicians are becoming interested in exploring the potential of cannabis-based medicines. Future targets will extend beyond symptom relief into disease modification, and already cannabinoids seem to offer particular promise in the treatment of certain inflammatory and neurodegenerative conditions. This chapter will begin with an outline of the development and current status of legal controls pertaining to cannabis, following which the existing human research will be reviewed. Some key safety issues will then be considered, and the chapter will conclude with some suggestions as to future directions for human research.

Monaldi Archives For Chest Disease • June 2005

Smoked marijuana as a cause of lung injury

By D.P. Tashkin

Division of Pulmonary & Critical Care Medicine, Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, CA 90095-1690, USA
dtashkin@mednet.ucla.edu

<http://www.ncbi.nlm.nih.gov/pubmed/16128224>

In many societies, marijuana is the second most commonly smoked substance after tobacco. While delta9-tetrahydrocannabinol (THC) is unique to marijuana and nicotine to tobacco, the smoke of marijuana, like that of tobacco, consists of a toxic mixture of gases and particulates, many of which are known to be harmful to the lung. Although far fewer marijuana than tobacco cigarettes are generally smoked on a daily basis, the pulmonary consequences of marijuana smoking may be magnified by the greater deposition of smoke particulates in the lung due to the differing manner in which marijuana is smoked. Whereas THC causes modest short-term bronchodilation, regular marijuana smoking produces a number of long-term pulmonary consequences, including chronic cough and sputum, histopathologic evidence of widespread airway inflammation and injury and immunohistochemical evidence of dysregulated growth of respiratory epithelial cells, that may be precursors to lung cancer. The THC in marijuana could contribute to some of these injurious changes through its ability to augment oxidative stress, cause mitochondrial dysfunction, and inhibit apoptosis. On the other hand, physiologic, clinical or epidemiologic evidence that marijuana smoking may lead to chronic obstructive pulmonary disease or respiratory cancer is limited and inconsistent. Habitual use of marijuana is also associated with abnormalities in the structure and function of alveolar macrophages, including impairment in microbial phagocytosis and killing that is associated with defective production of immunostimulatory cytokines and nitric oxide, thereby potentially predisposing to pulmonary infection. In view of the growing interest in medicinal marijuana, further epidemiologic studies are needed to clarify the true risks of regular marijuana smoking on respiratory health.

Proceedings Of The National Academy Of Science USA • June 2005

Altering cannabinoid signaling during development disrupts neuronal activity

Bernard C1, Milh M, Morozov YM, Ben-Ari Y, Freund TF, Gozlan H.

Institut de Neurobiologie de la Méditerranée-Institut National de la Santé et de la Recherche Médicale U29, 163 Route de Luminy BP13, 13273 Marseille Cédex 09, France

Full text with 34 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1166590/>

In adult cortical tissue, recruitment of GABAergic inhibition prevents the progression of synchronous population discharges to epileptic activity. However, at early developmental stages, GABA is excitatory and thus unable to fulfill this role. Here, we report that retrograde signaling involving endocannabinoids is responsible for the homeostatic control of synaptic transmission and the resulting network patterns in the immature hippocampus. Blockade of cannabinoid type 1 (CB1) receptor led to epileptic discharges, whereas overactivation of CB1 reduced network activity *in vivo*. Endocannabinoid signaling thus is able to keep population discharge patterns within a narrow physiological time window, balancing between epilepsy on one side and sparse activity on the other, which may result in impaired developmental plasticity. Disturbing this delicate balance during pregnancy in either direction, e.g., with marijuana as a CB1 agonist or with an antagonist marketed as an antiobesity drug, can have profound consequences for brain maturation even in human embryos.

General and oral health implications of cannabis use

Cho CM1, Hirsch R, Johnstone S.

Dental School, The University of Adelaide, South Australia
choi.cho@student.adelaide.edu.au

Full text, PDF, with 32 references

<http://onlinelibrary.wiley.com/doi/10.1111/j.1834-7819.2005.tb00343.x/epdf>

Cannabis, commonly known as marijuana, is the most frequently used illicit drug in Australia. Therefore, oral health care providers are likely to encounter patients who are regular users. An upward trend in cannabis use is occurring in Australia, with 40 per cent of the population aged 14 and above having used the drug. There are three main forms of cannabis: marijuana, hash and hash oil, all of which contain the main psychoactive constituent delta-9-tetrahydrocannabinol (THC). Cannabis is most commonly smoked, however it can be added to foods. THC from cannabis enters the bloodstream and exerts its effects on the body via interaction with endogenous receptors. Cannabis affects almost every system of the body, particularly the cardiovascular, respiratory and immune systems. It also has acute and chronic effects on the mental health of some users. Therefore, chronic abuse is a concern because of its negative effects on general physical and mental health. Cannabis abusers generally have poorer oral health than non-users, with an increased risk of dental caries and periodontal diseases. Cannabis smoke acts as a carcinogen and is associated with dysplastic changes and pre-malignant lesions within the oral mucosa. Users are also prone to oral infections, possibly due to the immunosuppressive effects. Dental treatment on patients intoxicated on cannabis can result in the patient experiencing acute anxiety, dysphoria and psychotic-like paranoid thoughts. The use of local anaesthetic containing epinephrine may seriously prolong tachycardia already induced by an acute dose of cannabis. Oral health care providers should be aware of the diverse adverse effects of cannabis on general and oral health and incorporate questions about patients' patterns of use in the medical history.

Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age

Gray KA1, Day NL, Leech S, Richardson GA.

Susceptibility and Population Health Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA

<http://www.ncbi.nlm.nih.gov/pubmed/15869861>

Studies of the consequences of prenatal marijuana use have reported effects predominantly on the behavioral and cognitive development of the children. Research on other aspects of child neurobehavioral development, such as psychiatric symptomatology, has been limited. This study examines the relations between prenatal marijuana exposure (PME) and child depressive symptoms at 10 years of age. Data are from the 10-year follow-up of 633 mother-child dyads who participated in the Maternal Health Practices and Child Development Project. Maternal prenatal and current substance use, measures of the home environment, demographic status, and psychosocial characteristics were ascertained at prenatal months four and seven, at delivery, and at age 10. At age 10, the children also completed the Children's Depression Inventory (CDI) [M. Kovacs. *The Children's Depression Inventory*, Multi-Health Systems, Inc., North Tonawanda, NY, (1992).], a self-report measure of current depressive symptoms. Multivariate regressions were used to test trimester-specific effects of marijuana and their associations with the CDI total score, while controlling for significant prenatal predictors and significant current covariates of childhood depression. PME in the first and third trimesters predicted significantly increased levels of depressive symptoms. This finding remained significant after controlling for all identified covariates from both the prenatal period and the current phase at age 10. These findings reflect an association with the level of depressive symptoms rather than a diagnosis of a major depressive disorder. Other significant correlates of depressive symptoms in the children included maternal education, maternal tobacco use (prenatal or current), and the child's composite IQ score. These findings are consistent with recent reports that identify specific areas of the brain and specific brain functions that are associated with PME.

Epidemiologic review of marijuana use and cancer risk

Hashibe M1, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF.

International Agency for Research on Cancer, 69008 Lyon, France

<http://www.ncbi.nlm.nih.gov/pubmed/16054989>

Marijuana is the most commonly used illegal drug in the United States and is considered by young adults to be the illicit drug with the least risk. On the other hand, marijuana smoke contains several of the same carcinogens and co-carcinogens as the tar from tobacco, raising concerns that smoking of marijuana may be a risk factor for tobacco-related cancers. We reviewed two cohort studies and 14 case-control studies with assessment of the association of marijuana use and cancer risk.

In the cohort studies, increased risks of lung or colorectal cancer due to marijuana smoking were not observed, but increased risks of prostate and cervical cancers among non-tobacco smokers, as well as adult-onset glioma among tobacco and non-tobacco smokers, were observed. The 14 case-control studies included four studies on head and neck cancers, two studies on lung cancer, two studies on non-Hodgkin's lymphoma, one study on anal cancer, one study on penile cancer, and four studies on childhood cancers with assessment of parental exposures. Zhang and colleagues reported that marijuana use may increase risk of head and neck cancers in a hospital-based case-control study in the United States, with dose-response relations for both frequency and duration of use. However, Rosenblatt and co-workers reported no association between oral cancer and marijuana use in a population-based case-control study. An eightfold increase in risk among marijuana users was

observed in a lung cancer study in Tunisia. However, there was no assessment of the dose response, and marijuana may have been mixed with tobacco. Parental marijuana use during gestation was associated with increased risks of childhood leukemia, astrocytoma, and rhabdomyosarcoma, but dose-response relations were not assessed.

In summary, sufficient studies are not available to adequately evaluate marijuana impact on cancer risk. Several limitations of previous studies include possible underreporting where marijuana use is illegal, small sample sizes, and too few heavy marijuana users in the study sample. Recommendations for future studies are to (1) focus on tobacco-related cancer sites; (2) obtain detailed marijuana exposure assessment, including frequency, duration, and amount of personal use as well as mode of use (smoked in a cigarette, pipe, or bong; taken orally); (3) adjust for tobacco smoking and conduct analyses on nonusers of tobacco; and (4) conduct larger studies, meta-analyses, or pooled analyses to maximize statistical precision and investigate sources of differences in results.

Despite the challenges, elucidation of the association between marijuana use and cancer risk is important in weighing the benefits and risks of medical marijuana use and to clarify the impact of marijuana use on public health.

Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation

Gruber SA1, Yurgelun-Todd DA.

Cognitive Neuroimaging Laboratory, Brain Imaging Center, McLean Hospital, Department of Psychiatry, Harvard Medical School, Belmont, MA 02478, USA
gryber@mclean.harvard.edu

<http://www.ncbi.nlm.nih.gov/pubmed/15795138>

Neuropsychological investigations of substance abusers have reported impairments on tasks mediated by the frontal executive system, including functions associated with behavioral inhibition and decision making. The higher order or executive components which are involved in decision making include selective attention and short term storage of information, inhibition of response to irrelevant information, initiation of response to relevant information, self-monitoring of performance, and changing internal and external contingencies in order to “stay the course” towards the ultimate goal. Given the hypothesized role of frontal systems in decision making and the previous evidence that executive dysfunctions and structural brain changes exist in subjects who use illicit drugs, we applied fMRI and diffusion tensor imaging (DTI) techniques in a pilot investigation of heavy cannabis smokers and matched control subjects while performing a modification of the classic Stroop task. Marijuana smokers demonstrated significantly lower anterior cingulate activity in focal areas of the anterior cingulate cortex and higher midcingulate activity relative to controls, although both groups were able to perform the task within normal limits. Normal controls also demonstrated increased activity within the right dorsolateral prefrontal cortex (DLPFC) during the interference condition, while marijuana smokers demonstrated a more diffuse, bilateral pattern of DLPFC activation. Similarly, although both groups performed the task well, marijuana smokers made more errors of commission than controls during the interference condition, which were associated with different brain regions than control subjects. These findings suggest that marijuana smokers exhibit different patterns of BOLD response and error response during the Stroop interference condition compared to normal controls despite similar task performance. Furthermore, DTI measures in frontal regions, which include the genu and splenium of the corpus callosum and bilateral anterior cingulate white matter regions, showed no between group differences in fractional anisotropy (FA), a measure of directional coherence within white matter fiber tracts, but a notable increase in trace, a measure of overall isotropic diffusivity in marijuana smokers compared to controls. Overall, results from the present study indicate significant differences in the magnitude and pattern of signal intensity change within the anterior cingulate and the DLPFC during the Stroop interference subtest in chronic marijuana smokers compared to normal controls. Furthermore, although chronic marijuana smokers were able to perform the task reasonably well, the functional activation findings suggest they utilize different cortical processes from the control subjects in order to do so. Findings from this study are consistent with the notion that substance abusers demonstrate evidence of altered frontal neural function during the performance of tasks that involve inhibition and performance monitoring, which may affect the ability to make decisions.

Cannabinoid CB1 receptor antagonists as promising new medications for drug dependence

Le Foll B1, Goldberg SR.

1. Preclinical Pharmacology Section, NIDA, NIH, 5500 Nathan Shock Drive, Baltimore, MD, USA
blefoll@intra.nida.nih.gov

Full text, PDF, with 110 references

<http://jpet.aspetjournals.org/content/312/3/875.full.pdf>

This review examines the development of cannabinoid CB(1) receptor antagonists as a new class of therapeutic agents for drug addiction. Abused drugs [alcohol, opiates, Delta(9)-tetrahydrocannabinol (Delta(9)-THC), and psychostimulants, including nicotine] elicit a variety of chronically relapsing disorders by interacting with endogenous neural pathways in the brain. In particular, they share the common property of activating mesolimbic dopamine brain reward systems, and virtually all abused drugs elevate dopamine levels in the nucleus accumbens. Cannabinoid CB(1) receptors are expressed in this brain reward circuit and modulate the dopamine-releasing effects of Delta(9)-THC and nicotine. Rimonabant (SR141716), a CB(1) receptor antagonist, blocks both the dopamine-releasing and discriminative and rewarding effects of Delta(9)-THC in animals. Blockade of CB(1) receptor activity by genetic invalidation also decreases rewarding effects of opiates and alcohol in animals. Although CB(1) receptor blockade is generally ineffective in reducing the self-administration of cocaine in rodents and primates, it reduces the reinstatement of extinguished cocaine-seeking behavior produced by cocaine-associated conditioned stimuli and cocaine-priming injections. Likewise, CB(1) receptor blockade is effective in reducing nicotine-seeking behavior induced by re-exposure to nicotine-associated stimuli. Some of these findings have been recently validated in humans. In clinical trials, Rimonabant blocks the subjective effects of Delta(9)-THC in humans and prevents relapse to smoking in exsmokers. Findings from both clinical and preclinical studies suggest that ligands blocking CB(1) receptors offer a novel approach for patients suffering from drug dependence that may be efficacious across different classes of abused drugs.

Brain effects of cannabis—neuroimaging findings

Crippa JA1, Lacerda AL, Amaro E, Busatto Filho G, Zuardi AW, Bressan RA.

Departamento de Neurologia, Psiquiatria e Psicologia Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Brazil
jcrippa@directnet.com.br

<http://www.ncbi.nlm.nih.gov/pubmed/15867988>

Cannabis is the most widely used illicit drug. Despite this, only a small number of studies have investigated the long-term neurotoxic consequences of cannabis use. Structural and functional neuroimaging techniques are powerful research tools to investigate possible cannabis-induced pathophysiological changes. A computer literature review was conducted in the MEDLINE and PsycLIT databases between 1966 and November of 2004 with the search terms 'cannabis', 'marijuana', 'neuroimaging', 'magnetic resonance', 'computed tomography', 'positron emission tomography', 'single photon emission computed tomography', 'SPET', 'MRI' and 'CT'. Structural neuroimaging studies have yielded conflicting results. Most studies report no evidence of cerebral atrophy or regional changes in tissue volumes, and one study suggested that long-term users who started regular use on early adolescence have cerebral atrophy as well as reduction in gray matter. However, several methodological shortcomings limit the interpretation of these results. Functional neuroimaging studies have reported increases in neural activity in regions that may be related with cannabis intoxication or mood-change effects (orbital and mesial frontal lobes, insula, and anterior cingulate) and decreases in activity of regions related with cognitive functions impaired during acute intoxication. The important question whether residual neurotoxic effects occur after prolonged and regular use of cannabis remains unclear, with no study addressing this question directly. Better designed neuroimaging studies, combined with cognitive evaluation, may be elucidative on this issue.

Pharmacological actions of cannabinoids

By R.G. Pertwee

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK
rgp@abdn.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/16596770>

Mammalian tissues express at least two types of cannabinoid receptor, CB1 and CB2, both G protein coupled. CB1 receptors are expressed predominantly at nerve terminals where they mediate inhibition of transmitter release. CB2 receptors are found mainly on immune cells, one of their roles being to modulate cytokine release. Endogenous ligands for these receptors (endocannabinoids) also exist. These are all eicosanoids; prominent examples include arachidonylethanolamide (anandamide) and 2-arachidonoyl glycerol. These discoveries have led to the development of CB1- and CB2-selective agonists and antagonists and of bioassays for characterizing such ligands. Cannabinoid receptor antagonists include the CB1-selective SR141716A, AM251, AM281 and LY320135, and the CB2-selective SR144528 and AM630. These all behave as inverse agonists, one indication that CB1 and CB2 receptors can exist in a constitutively active state. Neutral cannabinoid receptor antagonists that seem to lack inverse agonist properties have recently also been developed. As well as acting on CB1 and CB2 receptors, there is convincing evidence that anandamide can activate transient receptor potential vanilloid type 1 (TRPV1) receptors. Certain cannabinoids also appear to have non-CB1, non-CB2, non-TRPV1 targets, for example CB2-like receptors that can mediate antinociception and "abnormal-cannabidiol" receptors that mediate vasorelaxation and promote microglial cell migration. There is evidence too for TRPV1-like receptors on glutamatergic neurons, for alpha2-adrenoceptor-like (imidazoline) receptors at sympathetic nerve terminals, for novel G protein-coupled receptors for R-(+)-WIN55212 and anandamide in the brain and spinal cord, for novel receptors for delta9-tetrahydrocannabinol and cannabinol on perivascular sensory nerves and for novel anandamide receptors in the gastro-intestinal tract. The presence of allosteric sites for cannabinoids on various ion channels and non-cannabinoid receptors has also been proposed. In addition, more information is beginning to emerge about the pharmacological actions of the non-psychoactive plant cannabinoid, cannabidiol. These recent advances in cannabinoid pharmacology are all discussed in this review.

Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation

Ramírez BG1, Blázquez C, Gómez del Pulgar T, Guzmán M, de Ceballos ML.

1. Neurodegeneration Group, Cajal Institute, Consejo Superior de Investigaciones Científicas, 28002 Madrid, Spain

Full text with 82 references

<http://www.jneurosci.org/content/25/8/1904.long>

Alzheimer's disease (AD) is characterized by enhanced beta-amyloid peptide (betaA) deposition along with glial activation in senile plaques, selective neuronal loss, and cognitive deficits. Cannabinoids are neuroprotective agents against excitotoxicity in vitro and acute brain damage in vivo. This background prompted us to study the localization, expression, and function of cannabinoid receptors in AD and the possible protective role of cannabinoids after betaA treatment, both in vivo and in vitro. Here, we show that senile plaques in AD patients express cannabinoid receptors CB1 and CB2, together with markers of microglial activation, and that CB1-positive neurons, present in high numbers in control cases, are greatly reduced in areas of microglial activation. In pharmacological experiments, we found that G-protein coupling and CB1 receptor protein expression are markedly decreased in AD brains. Additionally, in AD brains, protein nitration is increased, and, more specifically, CB1 and CB2 proteins show enhanced nitration. Intracerebroventricular administration of the synthetic cannabinoid WIN55,212-2 to rats prevent betaA-induced microglial activation, cognitive impairment, and loss of neuronal markers. Cannabinoids (HU-210, WIN55,212-2, and JWH-133) block betaA-induced activation of cultured microglial cells, as judged by mitochondrial activity, cell morphology, and tumor necrosis factor-alpha release; these effects are independent of the antioxidant action of cannabinoid compounds and are also exerted by a CB2-selective agonist. Moreover, cannabinoids abrogate microglia-mediated neurotoxicity after betaA addition to rat cortical cocultures. Our results indicate that cannabinoid receptors are important in the pathology of AD and that cannabinoids succeed in preventing the neurodegenerative process occurring in the disease.

Blood • February 2005

Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway

Powles T1, te Poele R, Shamash J, Chaplin T, Propper D, Joel S, Oliver T, Liu WM.

New Drug Study Group, St. Bartholomew's Hospital, London, UK

Full text with 37 references

<http://www.bloodjournal.org/content/105/3/1214.long?sso-checked=true>

Delta9-Tetrahydrocannabinol (THC) is the active metabolite of cannabis. THC causes cell death in vitro through the activation of complex signal transduction pathways. However, the role that the cannabinoid 1 and 2 receptors (CB1-R and CB2-R) play in this process is less clear. We therefore investigated the role of the CB-Rs in mediating apoptosis in 3 leukemic cell lines and performed microarray and immunoblot analyses to establish further the mechanism of cell death. One of the most intriguing findings was that THC-induced cell death was preceded by significant changes in the expression of genes involved in the mitogen-activated protein kinase (MAPK) signal transduction pathways. Both apoptosis and gene expression changes were altered independent of p53 and the CB-Rs.

Clinical Neuroscience Research • January 2005

Cannabis and endocannabinoid modulators: Therapeutic promises and challenges

Grant I1, Cahn BR.

Department of Psychiatry, University of California San Diego, Center for Medicinal Cannabis Research, 9500 Gilman Drive, La Jolla, CA 92093-0680, USA

Full text with 138 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2544377/>

The discovery that botanical cannabinoids such as delta-9 tetrahydrocannabinol exert some of their effect through binding specific cannabinoid receptor sites has led to the discovery of an endocannabinoid signaling system, which in turn has spurred research into the mechanisms of action and addiction potential of cannabis on the one hand, while opening the possibility of developing novel therapeutic agents on the other. This paper reviews current understanding of CB1, CB2, and other possible cannabinoid receptors, their arachidonic acid derived ligands (e.g. anandamide; 2 arachidonoyl glycerol), and their possible physiological roles. CB1 is heavily represented in the central nervous system, but is found in other tissues as well; CB2 tends to be localized to immune cells. Activation of the endocannabinoid system can result in enhanced or dampened activity in various neural circuits depending on their own state of activation. This suggests that one function of the endocannabinoid system may be to maintain steady state. The therapeutic action of botanical cannabis or of synthetic molecules that are agonists, antagonists, or which may otherwise modify endocannabinoid metabolism and activity indicates they may have promise as neuroprotectants, and may be of value in the treatment of certain types of pain, epilepsy, spasticity, eating disorders, inflammation, and possibly blood pressure control.

Altered brain tissue composition in heavy marijuana users

Matochik JA¹, Eldreth DA, Cadet JL, Bolla KI.

1. Intramural Research Program, Neuroimaging Research Branch, National Institute on Drug Abuse, NIH/DHHS, 5500 Nathan Shock Drive, Baltimore, MD 21224-6823, USA
jmatochi@intra.nida.nih.gov

<http://www.ncbi.nlm.nih.gov/pubmed/15607838>

Marijuana is the most widely used illicit substance in the United States; however, previous imaging studies have not detected altered brain structure in marijuana users compared to non-users. Voxel-based morphometry was used to investigate possible differences in brain tissue composition in a group of 11 heavy marijuana users and a group of 8 non-users. All participants were male. Statistical comparisons were made at the voxel level on T1-weighted magnetic resonance images to determine differences in gray matter and white matter tissue density. Compared to non-users, marijuana users had lower gray matter density in a cluster of voxels in the right parahippocampal gyrus ($P = 0.0001$), and greater density bilaterally near the precentral gyrus and the right thalamus ($P < 0.04$). Marijuana users also had lower white matter density in the left parietal lobe ($P = 0.03$), and higher density around the parahippocampal and fusiform gyri on the left side compared to non-users ($P < 0.002$). Longer duration of marijuana use (in years) was significantly correlated with higher white matter tissue density in the left precentral gyrus ($P = 0.045$). Our preliminary results suggest evidence of possible structural differences in the brain of heavy marijuana users, and localize regions for further investigation of the effects of marijuana in the brain.

La Revue du Praticien • January 2005

Adverse effects of marijuana

Mallaret M1, Dal'Bo-Rohrer D, Demattéis M.

1. Centre d'évaluation et d'information sur la pharmacodépendance, CHU Grenoble, 38043 Grenoble
mmallaret@chu-grenoble.fr

europepmc.org/abstract/med/15801396

When admitted in an emergency unit, young patients often present acute neurological effects of smoked marijuana. Other chronic adverse effects of marijuana are probably underestimated: postural syncope, arteritis, chronic bronchitis, amnesia. Marijuana may trigger a myocardial infarction and have a vasospastic effect. Marijuana has impairing effects on driving ability. Smoked marijuana is a potential respiratory tract carcinogen.

Phytochemical Analysis: PCA • January 2005

Flavonoid glycosides and cannabinoids from the pollen of *Cannabis sativa* L.

Ross SA1, ElSohly MA, Sultana GN, Mehmedic Z, Hossain CF, Chandra S.

1. National Center for Natural Products Research, University of Mississippi, University, Mississippi 38677-1848, USA
sross@olemiss.edu

<http://www.ncbi.nlm.nih.gov/pubmed/15688956>

Chemical investigation of the pollen grain collected from male plants of *Cannabis sativa* L. resulted in the isolation for the first time of two flavonol glycosides from the methanol extract, and the identification of 16 cannabinoids in the hexane extract. The two glycosides were identified as kaempferol 3-O-sophoroside and quercetin 3-O-sophoroside by spectroscopic methods including high-field two-dimensional NMR experiments. The characterisation of each cannabinoid was performed by GC-FID and GC-MS analyses and by comparison with both available reference cannabinoids and reported data. The identified cannabinoids were delta9-tetrahydrocannabinol, cannabidivarin, cannabicitran, delta9-tetrahydrocannabivarin, cannabicyclol, cannabidiol, cannabichromene, delta9-tetrahydrocannabinol, cannabigerol, cannabinol, dihydrocannabinol, cannabielsoin, 6a, 7, 10a-trihydroxytetrahydrocannabinol, 9, 10-epoxycannabitriol, 10-O-ethylcannabitriol, and 7, 8-dehydro-10-O-ethylcannabitriol.

Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats

O'Shea M1, Singh ME, McGregor IS, Mallet PE.

<http://www.ncbi.nlm.nih.gov/pubmed/15582916>

Although many studies have examined the acute behavioural effects of cannabinoids in rodents, few have examined the lasting effects of cannabinoids at different developmental ages. This study compared lasting effects of cannabinoid exposure occurring in adolescence to that occurring in early adulthood. Forty, 30-day old (adolescent) and 18, 56-day old (adult) female albino Wistar rats were injected with vehicle or incremental doses of the cannabinoid receptor agonist (-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl) cyclohexanol (CP 55,940) once per day for 21 consecutive days (150, 200 and 300 microg/kg i.p. for 3, 8 and 10 days, respectively). Following a 21-day drug-free period, working memory was assessed using an object recognition task. Locomotor activity was also measured in the object recognition apparatus via a ceiling-mounted passive infrared sensor. Three days later, anxiety was assessed using a social interaction test. In the object recognition task, significantly poorer working memory was observed in the adolescent but not adult CP 55,940-treated rats. Adolescent, but not adult CP 55,940-treated rats, also exhibited a significant decrease in social interaction with a novel conspecific. These results suggest that chronic exposure to a cannabinoid receptor agonist well after the immediate postnatal period, but before reaching sexual maturity, can lead to increased anxiety and a lasting impairment of working memory.

Nature Reviews • Drug Discovery • September 2004

The endocannabinoid system and its therapeutic exploitation

Di Marzo V1, Bifulco M, De Petrocellis L.

1. Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council, Via Campi Flegrei 34, Comprensorio Olivetti, 80078 Pozzuoli, Napoli, Italy
vdimarzo@icmib.na.cnr.it

<http://www.ncbi.nlm.nih.gov/pubmed/15340387>

The term 'endocannabinoid' - originally coined in the mid-1990s after the discovery of membrane receptors for the psychoactive principle in Cannabis, Delta9-tetrahydrocannabinol and their endogenous ligands - now indicates a whole signalling system that comprises cannabinoid receptors, endogenous ligands and enzymes for ligand biosynthesis and inactivation. This system seems to be involved in an ever-increasing number of pathological conditions. With novel products already being aimed at the pharmaceutical market little more than a decade since the discovery of cannabinoid receptors, the endocannabinoid system seems to hold even more promise for the future development of therapeutic drugs. We explore the conditions under which the potential of targeting the endocannabinoid system might be realized in the years to come.

Toxicon • September 2004

The good and the bad effects of (–) trans-delta-9-tetrahydrocannabinol (Δ 9-THC) on humans

By E.A. Carlini

Department of Psychobiology, Federal University of São Paulo, Paulista School of Medicine, Rua Botucatu, 862-1º andar—Ed. Ciências Biomédicas 04023-062-São Paulo-SP, Brazil

<http://www.sciencedirect.com/science/article/pii/S0041010104001965>

This review analyses the therapeutic usefulness of Δ 9-tetrahydrocannabinol and its potential to induce adverse reactions on humans. During the last 30 years an enormous amount of research was carried out resulting in the disclosure of the cannabinoid system in Central Nervous System, with its CB1 and CB2 receptors, and the agonist anandamide. Under the clinical point of view, Δ 9-THC produces some therapeutic benefits which are beyond reasonable doubt. Thus, the effects on nausea/emesis due to cancer chemotherapy, as appetite promoter, on some painful conditions and on symptoms of multiple sclerosis are clearly demonstrated.

Δ 9-THC is not devoid of ill effects. On the cognitive domain it impairs the human capacity to discriminate time intervals and space distances, vigilance, memory and the performance for mental work. On the psychic area Δ 9-THC may induce unpleasant reactions such as disconnected thoughts, panic reactions, disturbing changes in perception, delusions and hallucinatory experiences. However, the long term effects on the psyche and cognition are not known as there are no reports of prolonged use of Δ 9-THC. Actually, it has been proposed by WHO that Δ 9-THC should be rescheduled to schedule IV of the United Nations Convention on Psychotropic Drugs, as it does not constitute a substantial risk to public health and its abuse is rare if at all.

Neuropharmacology • September 2004

Hypothesis: cannabinoid therapy for the treatment of gliomas?

Velasco G1, Galve-Roperh I, Sánchez C, Blázquez C, Guzmán M.

1. Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Avenida Complutense, 28040 Madrid, Spain

<http://www.ncbi.nlm.nih.gov/pubmed/17952650>

Gliomas, in particular glioblastoma multiforme or grade IV astrocytoma, are the most frequent class of malignant primary brain tumours and one of the most aggressive forms of cancer. Current therapeutic strategies for the treatment of glioblastoma multiforme are usually ineffective or just palliative. During the last few years, several studies have shown that cannabinoids—the active components of the plant *Cannabis sativa* and their derivatives—slow the growth of different types of tumours, including gliomas, in laboratory animals. Cannabinoids induce apoptosis of glioma cells in culture via sustained ceramide accumulation, extracellular signal-regulated kinase activation and Akt inhibition. In addition, cannabinoid treatment inhibits angiogenesis of gliomas in vivo. Remarkably, cannabinoids kill glioma cells selectively and can protect non-transformed glial cells from death. These and other findings reviewed here might set the basis for a potential use of cannabinoids in the management of gliomas.

Drugs Today • August 2004

Towards cannabis and cannabinoid treatment of multiple sclerosis

Croxford JL1, Miller SD.

Department of Microbiology and Immunology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, USA

<http://www.ncbi.nlm.nih.gov/pubmed/15510238>

Multiple sclerosis is a common human demyelinating disease of the central nervous system (CNS), and it is thought to involve autoimmune responses to CNS myelin antigens. Current symptomatic therapies for multiple sclerosis are in some cases ineffective and may have a high risk of serious side effects. This has led some multiple sclerosis patients to self-medicate with cannabis, which anecdotal evidence suggests may be beneficial in controlling symptoms such as spasticity, pain, tremor and bladder dysfunction. In support of these claims, results from experimental studies have suggested that cannabinoid-based treatments may be beneficial in a wide number of diseases. Furthermore, recent research in animal models of multiple sclerosis has demonstrated the efficacy of cannabinoids in controlling disease-induced symptoms such as spasticity and tremor, as well as in ameliorating the severity of clinical disease. However, these initially promising results have not yet been fully translated into the clinic. Although cannabinoid treatment of multiple sclerosis symptoms has been shown to be both well tolerated and effective in a number of subjective tests in several small-scale clinical trials, objective measures demonstrating the efficacy of cannabinoids are still lacking. Currently, a number of large-scale phase III clinical trials are under way to further elucidate the use of cannabinoids in the symptomatic treatment of multiple sclerosis. This review highlights the recent advances in our understanding of the endocannabinoid system, discusses both the experimental and clinical evidence for the use of cannabinoids to treat multiple sclerosis and explores possible future strategies of cannabinoid therapy in multiple sclerosis.

Adverse effects of cannabis on health: an update of the literature since 1996

By H. Kalant

Department of Pharmacology, Medical Sciences Building, University of Toronto, Toronto, ON, Canada
harold.kalant@utoronto.ca

<http://www.ncbi.nlm.nih.gov/pubmed/15363608>

Recent research has clarified a number of important questions concerning adverse effects of cannabis on health. A causal role of acute cannabis intoxication in motor vehicle and other accidents has now been shown by the presence of measurable levels of Delta(9)-tetrahydrocannabinol (THC) in the blood of injured drivers in the absence of alcohol or other drugs, by surveys of driving under the influence of cannabis, and by significantly higher accident culpability risk of drivers using cannabis. Chronic inflammatory and precancerous changes in the airways have been demonstrated in cannabis smokers, and the most recent case-control study shows an increased risk of airways cancer that is proportional to the amount of cannabis use. Several different studies indicate that the epidemiological link between cannabis use and schizophrenia probably represents a causal role of cannabis in precipitating the onset or relapse of schizophrenia. A weaker but significant link between cannabis and depression has been found in various cohort studies, but the nature of the link is not yet clear. A large body of evidence now demonstrates that cannabis dependence, both behavioral and physical, does occur in about 7-10% of regular users, and that early onset of use, and especially of weekly or daily use, is a strong predictor of future dependence. Cognitive impairments of various types are readily demonstrable during acute cannabis intoxication, but there is no suitable evidence yet available to permit a decision as to whether long-lasting or permanent functional losses can result from chronic heavy use in adults. However, a small but growing body of evidence indicates subtle but apparently permanent effects on memory, information processing, and executive functions, in the offspring of women who used cannabis during pregnancy. In total, the evidence indicates that regular heavy use of cannabis carries significant risks for the individual user and for the health care system.

A novel component of cannabis extract potentiates excitatory synaptic transmission in rat olfactory cortex in vitro

Whalley BJ1, Wilkinson JD, Williamson EM, Constanti A.

Department of Pharmacology, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

<http://www.ncbi.nlm.nih.gov/pubmed/15234473>

Cannabis is a potential treatment for epilepsy, although the few human studies supporting this use have proved inconclusive. Previously, we showed that a standardized cannabis extract (SCE), isolated Delta9-tetrahydrocannabinol (Delta9-THC), and even Delta9-THC-free SCE inhibited muscarinic agonist-induced epileptiform bursting in rat olfactory cortical brain slices, acting via CB1 receptors. The present work demonstrates that although Delta9-THC (1 microM) significantly depressed evoked depolarizing postsynaptic potentials (PSPs) in rat olfactory cortex neurones, both SCE and Delta9-THC-free SCE significantly potentiated evoked PSPs (all results were fully reversed by the CB1 receptor antagonist SR141716A, 1 microM); interestingly, the potentiation by Delta9-THC-free SCE was greater than that produced by SCE. On comparing the effects of Delta9-THC-free SCE upon evoked PSPs and artificial PSPs (aPSPs; evoked electrotonically following brief intracellular current injection), PSPs were enhanced, whereas aPSPs were unaffected, suggesting that the effect was not due to changes in background input resistance. Similar recordings made using CB1 receptor-deficient knockout mice (CB1^{-/-}) and wild-type littermate controls revealed cannabinoid or extract-induced changes in membrane resistance, cell excitability and synaptic transmission in wild-type mice that were similar to those seen in rat neurones, but no effect on these properties were seen in CB1^{-/-} cells. It appears that the unknown extract constituent(s) effects over-rode the suppressive effects of Delta9-THC on excitatory neurotransmitter release, which may explain some patients' preference for herbal cannabis rather than isolated Delta9-THC (due to attenuation of some of the central Delta9-THC side effects) and possibly account for the rare incidence of seizures in some individuals taking cannabis recreationally.

Drug And Alcohol Review • June 2004

Pot, politics and the press—reflections on cannabis law reform in Western Australia

By S. Lenton

National Drug Research Institute, Curtin University of Technology, Perth, Western Australia, Australia
s.lenton@curtin.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/15370030>

Windows of opportunity for changing drug laws open infrequently and they often close without legislative change being affected. In this paper the author, who has been intimately involved in the process, describes how evidence-based recommendations to 'decriminalize' cannabis have recently been progressed through public debate and the political process to become law in Western Australia (WA). The Cannabis Control Bill 2003 passed the WA Parliament on 23 September. The Bill, the legislative backing behind the Cannabis Infringement Notice (CIN) Scheme, came into effect on 22 March 2004. This made WA the fourth Australian jurisdiction, after South Australia, the Australian Capital Territory and the Northern Territory, to adopt a prohibition with civil penalties scheme for minor cannabis offences. This paper describes some of the background to the scheme, the process by which it has become law, the main provisions of the scheme and its evaluation. It includes reflections on the role of politics and the press in the process. The process of implementation and evaluation are outlined by the author, foreshadowing an ongoing opportunity to understand the impact of the change in legislation.

A methodological and substantive review of the evidence that schools cause pupils to smoke

Aveyard P1, Markham WA, Cheng KK.

Department of Public Health and Epidemiology, The University of Birmingham, Birmingham B15 2TT, UK
p.n.aveyard@bham.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/15047082>

The objectives of this review were to examine whether smoking prevalence varies between schools independently of health promotion programmes and pupil composition, to show which school characteristics are responsible for this variation, and to examine the methodological adequacy of such studies. Searches for published studies were performed on medical, educational and social science databases, relevant articles' reference lists, and citation searches. Any study was included that described inter-school variation in smoking prevalence, or related such variation to school characteristics. A model relating pupil smoking to school, neighbourhood, and pupil characteristics unlikely and likely to be influenced by school was used to examine the adequacy of control of confounding by pupil composition. Data from studies were combined qualitatively considering methodological adequacy to examine the relation of smoking prevalence to school characteristics. Theoretical frameworks underpinning the choice of school characteristics and postulated relationships between these characteristics and smoking prevalence were described. There were large variations in smoking prevalence between ostensibly similar schools. Evidence that pupil composition did not cause this was weak, because all studies had methodological problems, including under control of relevant pupil compositional factors and over control of factors likely to represent the mechanism through which schools influence pupils' smoking. There was little evidence that elements of tobacco control policy other than bans and enforcement deterred smoking. Academic practice and school ethos were related to smoking. Academically selective schools did not influence smoking, once pupil composition was controlled. There was one study on neighbourhood influences, which were unrelated to smoking. Studies frequently offered little or no theoretical justification for associating school characteristics with smoking. Some aspects of school influence pupils' smoking, probably independently of pupil composition. However, under-control and over-control of confounding and lack of theoretical underpinning precludes definitive conclusions on how particular school characteristics influence pupils' smoking.

Human skin permeation of Delta8-tetrahydrocannabinol, cannabidiol and cannabinol

Stinchcomb AL1, Valiveti S, Hammell DC, Ramsey DR.

1. Division of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536-0082, USA
astin2@email.uky.edu

<http://www.ncbi.nlm.nih.gov/pubmed/15025853>

The purpose of this study was to quantify the in-vitro human skin transdermal flux of Delta8-tetrahydrocannabinol (Delta8-THC), cannabidiol (CBD) and cannabinol (CBN). These cannabinoids are of interest because they are likely candidates for transdermal combination therapy. Differential thermal analysis and in-vitro diffusion studies with human tissue were completed for the compounds. Heats of fusion, melting points and relative thermodynamic activities were determined for the crystalline compounds, CBD and CBN. Flux, permeability, tissue concentration and lag times were measured in the diffusion experiments. CBN had a lower heat of fusion and corresponding higher calculated relative thermodynamic activity than CBD. Ethanol concentrations of 30 to 33% significantly increased the transdermal flux of Delta8-THC and CBD. Tissue concentrations of Delta8-THC were significantly higher than for CBN. Lag times for CBD were significantly smaller than for CBN. The permeabilities of CBD and CBN were 10-fold higher than for Delta8-THC. Combinations of these cannabinoids with ethanol will be further studied in transdermal patch formulations in vitro and in vivo, as significant flux levels of all the drugs were obtained. CBD, the most polar of the three drugs, and other more polar cannabinoids will also be the focus of future drug design studies for improved transdermal delivery rates.

Neuro Endocrinology Letters • February 2004

On the application of cannabis in paediatrics and epileptology

By R. Lorenz
ruelor@t-online.de

<http://www.ncbi.nlm.nih.gov/pubmed/15159680>

An initial report on the therapeutic application of delta 9-THC (THC) (Dronabinol, Marinol) in 8 children resp. adolescents suffering from the following conditions, is given: neurodegenerative disease, mitochondriopathy, posthypoxic state, epilepsy, posttraumatic reaction. THC effected reduced spasticity, improved dystonia, increased initiative (with low dose), increased interest in the surroundings, and anticonvulsive action. The doses ranged from 0.04 to 0.12 mg/kg body weight a day. The medication was given as an oily solution orally in 7 patients, via percutaneous gastroenterostomy tube in one patient. At higher doses disinhibition and increased restlessness were observed. In several cases treatment was discontinued and in none of them discontinuing resulted in any problems. The possibility that THC-induced effects on ion channels and transmitters may explain its therapeutic activity seen in epileptic patients is discussed.

Effects of cannabidiol (CBD) on regional cerebral blood flow

Crippa JA1, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE, McGuire PK, Filho Busatto G.

1. Department of Neuropsychiatry and Medical Psychology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil

Full text with 115 references

<http://www.nature.com/npp/journal/v29/n2/full/1300340a.html>

Animal and human studies have suggested that cannabidiol (CBD) may possess anxiolytic properties, but how these effects are mediated centrally is unknown. The aim of the present study was to investigate this using functional neuroimaging. Regional cerebral blood flow (rCBF) was measured at rest using (99m)Tc-ECD SPECT in 10 healthy male volunteers, randomly divided into two groups of five subjects. Each subject was studied on two occasions, 1 week apart. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. SPECT images were acquired 90 min after drug ingestion. The Visual Analogue Mood Scale was applied to assess subjective states. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using statistical parametric mapping (SPM). CBD significantly decreased subjective anxiety and increased mental sedation, while placebo did not induce significant changes. Assessment of brain regions where anxiolytic effects of CBD were predicted a priori revealed two voxel clusters of significantly decreased ECD uptake in the CBD relative to the placebo condition ($p < 0.001$, uncorrected for multiple comparisons). These included a medial temporal cluster encompassing the left amygdala-hippocampal complex, extending into the hypothalamus, and a second cluster in the left posterior cingulate gyrus. There was also a cluster of greater activity with CBD than placebo in the left parahippocampal gyrus ($p < 0.001$). These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas.

Cannabinoid pharmacology in the cardiovascular system: potential protective mechanisms through lipid signalling

Hiley CR1, Ford WR.

Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge CB2 1PD, UK
crh1@cam.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/15005177>

Cannabinoids include not only plant-derived compounds (of which delta9-tetrahydrocannabinol is the primary psychoactive ingredient of cannabis), but also synthetic agents and endogenous substances termed endocannabinoids which include anandamide (2-arachidonoyl ethanolamide) and 2-arachidonoylglycerol. Cannabinoids act on specific, G-protein-coupled, receptors which are currently divided into two types, CB1 and CB2. Relatively selective agonists and antagonists for these receptors have been developed, although one agent (SR141716A) widely used as an antagonist at CB1 receptors has non-cannabinoid receptor-mediated effects at concentrations which are often used to define the presence of the CB1 receptor. Both cannabinoid receptors are primarily coupled to Gi/o proteins and act to inhibit adenylyl cyclase. Stimulation of CB1 receptors also modulates the activity of K⁺ and Ca²⁺ channels and of protein kinase pathways including protein kinase B (Akt) which might mediate effects on apoptosis. CB₁ receptors may activate the extracellular signal-regulated kinase cascade through ceramide signalling. Cannabinoid actions on the cardiovascular system have been widely interpreted as being mediated by CB1 receptors although there are a growing number of observations, particularly in isolated heart and blood vessel preparations, that suggest that other cannabinoid receptors may exist. Interestingly, the currently identified cannabinoid receptors appear to be related to a wider family of lipid receptor, those for the lysophospholipids, which are also linked to Gi/o protein signalling. Anandamide also activates vanilloid VR1 receptors on sensory nerves and releases the vasoactive peptide, calcitonin gene-related peptide (CGRP), which brings about vasodilatation through its action on CGRP receptors. Current evidence suggests that endocannabinoids have important protective roles in pathophysiological conditions such as shock and myocardial infarction. Therefore, their cardiovascular effects and the receptors mediating them are the subject of increasing investigative interest.

Therapeutic potential of cannabinoids in CNS disease

By J.L. Croxford

Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois 60610, USA
j-croxford@northwestern.edu

<http://www.ncbi.nlm.nih.gov/pubmed/12617697>

The major psychoactive constituent of *Cannabis sativa*, delta(9)-tetrahydrocannabinol (delta(9)-THC), and endogenous cannabinoid ligands, such as anandamide, signal through G-protein-coupled cannabinoid receptors localised to regions of the brain associated with important neurological processes. Signaling is mostly inhibitory and suggests a role for cannabinoids as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial. Anecdotal evidence suggests that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms. Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis, and clinical trials of the use of these compounds for these symptoms are in progress. The cannabinoid nabilone is currently licensed for use as an antiemetic agent in chemotherapy-induced emesis. Evidence suggests that cannabinoids may prove useful in Parkinson's disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents. Dexanabinol (HU-211), a synthetic cannabinoid, is currently being assessed in clinical trials for traumatic brain injury and stroke. Animal models of mechanical, thermal and noxious pain suggest that cannabinoids may be effective analgesics. Indeed, in clinical trials of postoperative and can-

cer pain and pain associated with spinal cord injury, cannabinoids have proven more effective than placebo but may be less effective than existing therapies. Dronabinol, a commercially available form of delta(9)-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity. Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that occur with existing therapeutic agents. The use of nonpsychoactive cannabinoids such as cannabidiol and dexanabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. The existence of other cannabinoid receptors may provide novel therapeutic targets that are independent of CB(1) receptors (at which most currently available cannabinoids act) and the development of compounds that are not associated with CB(1) receptor-mediated adverse effects. Further understanding of the most appropriate route of delivery and the pharmacokinetics of agents that act via the endocannabinoid system may also reduce adverse effects and increase the efficacy of cannabinoid treatment. This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment. Where applicable, reference is made to ongoing clinical trials of cannabinoids to alleviate symptoms of these disorders.

**Cannabis-based medicines—
GW pharmaceuticals: high CBD, high THC, medicinal cannabis—
GW pharmaceuticals, THC:CBD**

[No authors listed]

<http://www.ncbi.nlm.nih.gov/pubmed/12952500>

GW Pharmaceuticals is undertaking a major research programme in the UK to develop and market distinct cannabis-based prescription medicines [THC:CBD, High THC, High CBD] in a range of medical conditions. The cannabis for this programme is grown in a secret location in the UK. It is expected that the product will be marketed in the US in late 2003. GW's cannabis-based products include selected phytocannabinoids from cannabis plants, including D9 tetrahydrocannabinol (THC) and cannabidiol (CBD). The company is investigating their use in three delivery systems, including sublingual spray, sublingual tablet and inhaled (but not smoked) dosage forms. The technology is protected by patent applications. Four different formulations are currently being investigated, including High THC, THC:CBD (narrow ratio), THC:CBD (broad ratio) and High CBD. GW is also developing a specialist security technology that will be incorporated in all its drug delivery systems. This technology allows for the recording and remote monitoring of patient usage to prevent any potential abuse of its cannabis-based medicines. GW plans to enter into agreements with other companies following phase III development, to secure the best commercialisation terms for its cannabis-based medicines. In June 2003, GW announced that exclusive commercialisation rights for the drug in the UK had been licensed to Bayer AG. The drug will be marketed under the Sativex brand name. This agreement also provides Bayer with an option to expand their license to include the

European Union and certain world markets. GW was granted a clinical trial exemption certificate by the Medicines Control Agency to conduct clinical studies with cannabis-based medicines in the UK. The exemption includes investigations in the relief of pain of neurological origin and defects of neurological function in the following indications: multiple sclerosis (MS), spinal cord injury, peripheral nerve injury, central nervous system damage, neuroinvasive cancer, dystonias, cerebral vascular accident and spina bifida, as well as for the relief of pain and inflammation in rheumatoid arthritis and also pain relief in brachial plexus injury. The UK Government stated that it would be willing to amend the Misuse of Drugs Act 1971 to permit the introduction of a cannabis-based medicine. GW stated in its 2002 Annual Report that it was currently conducting five phase III trials of its cannabis derivatives, including a double-blind, placebo-controlled trial with a sublingual spray containing High THC in more than 100 patients with cancer pain in the UK. Also included is a phase III trial of THC:CBD (narrow ratio) being conducted in patients with severe pain due to brachial plexus injury, as are two more phase III trials of THC:CBD (narrow ratio) targeting spasticity and bladder dysfunction in multiple sclerosis patients. Another phase III trial of THC:CBD (narrow ratio) in patients with spinal cord injury is also being conducted. Results from the trials are expected during 2003. Three additional trials are also in the early stages of planning. These trials include a phase I trial

of THC:CBD (broad ratio) in patients with inflammatory bowel disease, a phase I trial of High CBD in patients with psychotic disorders such as schizophrenia, and a preclinical trial of High CBD in various CNS disorders (including epilepsy, stroke and head injury). GW Pharmaceuticals submitted an application for approval of cannabis-based medicines to UK regulatory authorities in March 2003. Originally GW hoped to market cannabis-based prescription medicines by 2004, but is now planning for a launch in the UK towards the end of 2003. Several trials for GW's cannabis derivatives have also been completed, including four randomised, double-blind, placebo-controlled phase III clinical trials conducted in the UK. The trials were initiated by GW in April 2002, to investigate the use of a sublingual spray containing THC:CBD (narrow ratio) in the following medical conditions: pain in spinal cord injury, pain and sleep in MS and spinal cord injury, neuropathic pain in MS and general neuropathic pain (presented as allodynia). Results from these trials show that THC:CBD (narrow ratio) caused statistically significant reductions in neuropathic pain in patients with MS and other conditions. In addition, improvements in

other MS symptoms were observed as well. Phase II studies of THC:CBD (narrow ratio) have also been completed in patients with MS, spinal cord injury, neuropathic pain and a small number of patients with peripheral neuropathy secondary to diabetes mellitus or AIDS. A phase II trial of THC:CBD (broad ratio) has also been completed in a small number of patients with rheumatoid arthritis, as has a trial of High CBD in patients with neurogenic symptoms. A phase II trial has also been evaluated with High THC in small numbers of patients for the treatment of perioperative pain. The phase II trials provided positive results and confirmed an excellent safety profile for cannabis-based medicines. GW Pharmaceuticals received an IND approval to commence phase II clinical trials in Canada in patients with chronic pain, multiple sclerosis and spinal cord injury in 2002. Following meetings with the US FDA, Drug Enforcement Agency (DEA), the Office for National Drug Control Policy, and National Institute for Drug Abuse, GW was granted an import license from the DEA and has imported its first cannabis extracts into the US. Preclinical research with these extracts in the US is ongoing.

Medicinal cannabis: is delta9-tetrahydrocannabinol necessary for all its effects?

Wilkinson JD1, Whalley BJ, Baker D, Pryce G, Constanti A, Gibbons S, Williamson EM.

Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London, 29/39 Brunswick Square, London, UK

<http://www.ncbi.nlm.nih.gov/pubmed/14738597>

Cannabis is under clinical investigation to assess its potential for medicinal use, but the question arises as to whether there is any advantage in using cannabis extracts compared with isolated Delta9-trans-tetrahydrocannabinol (Delta9THC), the major psychoactive component. We have compared the effect of a standardized cannabis extract (SCE) with pure Delta9THC, at matched concentrations of Delta9THC, and also with a Delta9THC-free extract (Delta9THC-free SCE), using two cannabinoid-sensitive models, a mouse model of multiple sclerosis (MS), and an in-vitro rat brain slice model of epilepsy. Whilst SCE inhibited spasticity in the mouse model of MS to a comparable level, it caused a more rapid onset of muscle relaxation, and a reduction in the time to maximum effect compared with Delta9THC alone. The Delta9THC-free extract or cannabidiol (CBD) caused no inhibition of spasticity. However, in the in-vitro epilepsy model, in which sustained epileptiform seizures were induced by the muscarinic receptor agonist oxotremorine-M in immature rat piriform cortical brain slices, SCE was a more potent and again more rapidly-acting anticonvulsant than isolated Delta9THC, but in this model, the Delta9THC-free extract also exhibited anticonvulsant activity. Cannabidiol did not inhibit seizures, nor did it modulate the activity of Delta9THC in this model. Therefore, as far as some actions of cannabis were concerned (e.g. antispasticity), Delta9THC was the active constituent, which might be modified by the presence of other components. However, for other effects (e.g. anticonvulsant properties) Delta9THC, although active, might not be necessary for the observed effect. Above all, these results demonstrated that not all of the therapeutic actions of cannabis herb might be due to the Delta9THC content.

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Cannabinoids: mechanisms and therapeutic applications in the CNS

Drysdale AJ1, Platt B.

Department of Biomedical Sciences, University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD, Scotland, UK
b.platt@abdn.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/14529462>

Cannabinoids comprise three classes of compounds, the active components of marijuana (*Cannabis sativa*), as well as endogenous and synthetic derivatives. To date, two distinct cannabinoid receptors (CB1 and CB2) have been discovered, but evidence for further receptor types has been brought forward. The potential use of cannabinoids for medicinal purposes has long been known, but the mechanisms of action of both exogenously applied and endogenous cannabinoids are only partly established. For nervous system disorders, cannabinoids may be useful by modulating neurotransmission and calcium homeostasis as well as by anti-inflammatory and anti-oxidant actions. Some cannabinoids can also trigger cell death, which may be of therapeutic benefit in the treatment of malignant tumours. A number of both *in vitro* and *in vivo* models have provided promising but diverse evidence for cannabinoid protection in glutamate-mediated excitotoxicity, hypoxia and glucose deprivation, brain trauma, epilepsy and MS. Subsequent to many preclinical investigations, clinical trials are now underway in a variety of the above applications. Overall, the understanding of the therapeutic relevance of cannabinoids will rely on further investigations into the neuroprotective and neurotoxic potency of cannabinoids in animal models and humans, as much as on a further advancement of our general understanding of the endocannabinoid system and the development of specific compounds devoid of unwanted psychoactive side effects.

Cannabinoids and memory: animal studies

Castellano C1, Rossi-Arnaud C, Cestari V, Costanzi M.

Istituto di Neuroscienze del CNR, Sezione di Psicobiologia e Psicofarmacologia, Viale Marx 15, 00137 Roma, Italy
c.castellano@ipsifar.rm.cnr.it

<http://www.ncbi.nlm.nih.gov/pubmed/14683467>

This review will consider studies concerning the effects of cannabinoid receptor agonists and antagonists on memory in laboratory animals. Two subtypes of cannabinoid receptors have been identified to date: the central CB1 subtype and the peripheral CB2 subtype. The receptor which specifically binds Delta9-tetrahydrocannabinol (Delta9-THC) and related compounds in rat and human brain has been discovered and cloned by a number of researchers. This cannabinoid receptor is localized with high concentrations in different brain areas, including hippocampus and amygdala, which play an important role in the modulation of memory. In recent years evidence has been obtained that cannabinoids influence memory processes. It has been shown, for example, that Delta9-THC impairs memory in rats, mice and monkeys tested in a variety of experimental conditions (radial maze, instrumental discrimination tasks, Morris water maze, etc.). In some of these researches the effect of Delta9-THC was antagonized by the CB1 receptor antagonist SR 141716A, showing the involvement of this subtype of cannabinoid receptor in its effect. Anandamide, arachidonylethanolamide, was recently discovered as the first endogenous ligand for the cannabinoid receptor. It has been reported to stimulate CB1 receptors and to mimic the pharmacological effects of cannabinoids. Experiments carried out by our group have shown that anandamide impairs memory consolidation in random bred mice (CD1), exerts genotype-dependent influences on memory in inbred strain of mice (C57 BL/6 and DBA/2), and that opioid and dopaminergic systems might be involved in its effects.

National Reviews In Cancer • October 2003

Cannabinoids: potential anticancer agents

By M. Guzmán

Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040 Madrid, Spain
mgp@bbm1.ucm.es

<http://www.ncbi.nlm.nih.gov/pubmed/27005465>

Cannabinoids - the active components of *Cannabis sativa* and their derivatives - exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating appetite. In addition, these compounds have been shown to inhibit the growth of tumour cells in culture and animal models by modulating key cell-signalling pathways. Cannabinoids are usually well tolerated, and do not produce the generalized toxic effects of conventional chemotherapies. So, could cannabinoids be used to develop new anticancer therapies?

Schmerz (Berlin, Germany) • October 2003

Therapeutic use of cannabinoids in neurology

Schwenkreis P1, Tegenthoff M.

Neurologische Universitätsklinik, BG-Kliniken Bergmannsheil Bochum
peter.schwenkreis@ruhr-uni-bochum.de

<http://www.ncbi.nlm.nih.gov/pubmed/14513344>

This review gives insight into the potential therapeutical role of cannabinoids in neurology. Preclinical data are presented which could give a rationale for the clinical use of cannabinoids in the fields of multiple sclerosis, spasticity, epilepsy, movement disorders, and neuroprotection after traumatic head injury or ischemic stroke. Besides, clinical data (case reports, open-label and randomised controlled studies) dealing with the therapeutical use of cannabinoids in these fields are reported and discussed. At present, clinical data are insufficient to recommend the use of cannabinoids in any neurological disease as standard therapy. Several questions still have to be answered (which cannabinoid? which way of administration? stimulation of endogenous cannabinoids? separation between desired and undesired effects?), and controlled studies are still needed to clarify the potential therapeutical role of cannabinoids in neurology.

Journal Of Health Economics • July 2003

Is cannabis a stepping-stone for cocaine?

By J.C. van Ours

Department of Economics and Center for Economic Research, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, The Netherlands
vanours@uvt.nl

<http://www.ncbi.nlm.nih.gov/pubmed/12842314>

This paper uses a unique dataset on the inhabitants of Amsterdam, to study the dynamics of the consumption of cannabis and cocaine. People are most likely to start using that drugs at ages 18-20 and 20-25. An analysis of the starting rates shows some evidence of cannabis being a “stepping-stone” for cocaine. However, the fact that some individuals use both cannabis and cocaine has to do mostly with correlation through (unobserved) personal characteristics and not with cannabis causing the use of cocaine.

Journal Of The American College Of Health • July 2003

**Trends in marijuana and other illicit drug use among college students:
results from 4 Harvard School of Public Health College Alcohol Study surveys: 1993-2001**

Mohler-Kuo M1, Lee JE, Wechsler H.

1. Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, MA 02115, USA

<http://www.ncbi.nlm.nih.gov/pubmed/14717576>

The authors examined changes in college students' illicit drug use, patterns of polydrug use, and the relationship between students' ages of initiation of substance use and later use of marijuana and other illicit drugs between 1993 and 2001. Data from 119 US colleges and universities in the Harvard School of Public Health College Alcohol Study were used in the study. They found significant increases in percentages of students' use of marijuana in the past 30 days (from 13% to 17%), past year (from 23% to 30%), and lifetime (from 41% to 47%) between 1993 and 2001, with most of the increase occurring between 1993 and 1997. Past 30-day use of other illicit drugs increased from 4% to 7% and past year use increased from 11% to 14%. More than 98% of marijuana and other illicit drug users used another substance. They also either smoked, were binge drinkers, and/or were users of another illicit drug. Drug prevention programs should emphasize heavy alcohol use and smoking and should start when students are in high school or earlier.

Physiological Reviews • July 2003

Role of Endogenous Cannabinoids in Synaptic Signaling

Tamas F. Freund, Istvan Katona, Daniele Piomelli

Full text, PDF, numerous photographic images and 381 references

<http://physrev.physiology.org/content/physrev/83/3/1017.full.pdf>

Research of cannabinoid actions was boosted in the 1990s by remarkable discoveries including identification of endogenous compounds with cannabimimetic activity (endocannabinoids) and the cloning of their molecular targets, the CB1 and CB2 receptors. Although the existence of an endogenous cannabinoid signaling system has been established for a decade, its physiological roles have just begun to unfold. In addition, the behavioral effects of exogenous cannabinoids such as delta-9-tetrahydrocannabinol, the major active compound of hashish and marijuana, await explanation at the cellular and network levels. Recent physiological, pharmacological, and high-resolution anatomical studies provided evidence that the major physiological effect of cannabinoids is the regulation of neurotransmitter release via activation of presynaptic CB1 receptors located on distinct types of axon terminals throughout the brain. Subsequent discoveries shed light on the functional consequences of this localization by demonstrating the involvement of endocannabinoids in retrograde signaling at GABAergic and glutamatergic synapses. In this review, we aim to synthesize recent progress in our understanding of the physiological roles of endocannabinoids in the brain. First, the synthetic pathways of endocannabinoids are discussed, along with the putative mechanisms of their release, uptake, and degradation. The fine-grain anatomical distribution of the neuronal cannabinoid receptor CB1 is described in most brain areas, emphasizing its general presynaptic localization and role in controlling neurotransmitter release. Finally, the possible functions of endocannabinoids as retrograde synaptic signal molecules are discussed in relation to synaptic plasticity and network activity patterns.

Medical Science Monitor • June 2003

Medical marijuana: should minors have the same rights as adults?

By P.A. Clark

Jesuit Community St. Joseph's University Philadelphia, Pennsylvania, USA
pclark@sju.edu

Full text, PDF, with 46 references

<http://www.medscimonit.com/download/index/idArt/12704>

After reviewing the pertinent scientific data, it is clear that there is more than sufficient medical and ethical evidence to warrant the Bush Administration to authorize the Drug Enforcement Agency to reclassify marijuana as a Schedule II drug so that it can be used for medical purposes. Failure to give an effective therapy to seriously ill patients, either adults or children, violates the core principles of both medicine and ethics. Medically, to deny physicians the right to prescribe to their patients a therapy that relieves pain and suffering violates the physician-patient relationship. Ethically, failure to offer an available therapy that has proven to be effective violates the basic ethical principle of nonmaleficence, which prohibits the infliction of harm, injury, or death and is related to the maxim *primum non nocere* ('above all, or first, do no harm'), which is widely used to describe the duties of a physician. Therefore, in the patient's best interest, patients and parents/surrogates, have the right to request medical marijuana under certain circumstances and physicians have the duty to disclose medical marijuana as an option and prescribe it when appropriate. The right to an effective medical therapy, whose benefits clearly outweigh the burdens, must be available to all patients including children. To deny children the use of medical marijuana when appropriate is a grave injustice which violates the basic foundational beliefs of both medicine and ethics.

Cannabis and the brain

By L. Iversen

The active compound in herbal cannabis, Delta(9)-tetrahydrocannabinol, exerts all of its known central effects through the CB(1) cannabinoid receptor. Research on cannabinoid mechanisms has been facilitated by the availability of selective antagonists acting at CB(1) receptors and the generation of CB(1) receptor knockout mice. Particularly important classes of neurons that express high levels of CB(1) receptors are GABAergic interneurons in hippocampus, amygdala and cerebral cortex, which also contain the neuropeptides cholecystinin. Activation of CB(1) receptors leads to inhibition of the release of amino acid and monoamine neurotransmitters. The lipid derivatives anandamide and 2-arachidonylglycerol act as endogenous ligands for CB(1) receptors (endocannabinoids). They may act as retrograde synaptic mediators of the phenomena of depolarization-induced suppression of inhibition or excitation in hippocampus and cerebellum. Central effects of cannabinoids include disruption of psychomotor behaviour, short-term memory impairment, intoxication, stimulation of appetite, antinociceptive actions (particularly against pain of neuropathic origin) and anti-emetic effects. Although there are signs of mild cognitive impairment in chronic cannabis users there is little evidence that such impairments are irreversible, or that they are accompanied by drug-induced neuropathology. A proportion of regular users of cannabis develop tolerance and dependence on the drug. Some studies have linked chronic use of cannabis with an increased risk of psychiatric illness, but there is little evidence for any causal link. The potential medical applications of cannabis in the treatment of painful muscle spasms and other symptoms of multiple sclerosis are currently being tested in clinical trials. Medicines based on drugs that enhance the function of endocannabinoids may offer novel therapeutic approaches in the future.

Effects of cannabinoids on CNS function Psychomotor control

CB1 receptors are expressed at particularly high densities in the basal ganglia and cerebellum, so it is not surprising that cannabinoids have complex effects on psychomotor function (reviewed by Rodríguez de Fonseca et al., 1998). One of the earliest reports of the effects of cannabis extracts in experimental animals described the awkward swaying and rolling gait caused by the drug in dogs, with periods of intense activity provoked by tactile or auditory stimuli, and followed eventually by catalepsy and sleep (Dixon, 1899). In rodents cannabinoids tend to have a triphasic effect. Thus in rats low doses of THC

(0.2 mg/kg) decreased locomotor activity, while higher doses (1–2 mg/kg) stimulated movements, and catalepsy emerged at doses of 2.5 mg/kg (Sañudo-Peña et al., 2000). Similarly in mice, Adams and Martin (1996) described a 'popcorn effect' in animals treated with THC. Groups of mice are sedated by the drug, but will jump in response to auditory or tactile stimuli, as they fall into other animals these in turn jump, resembling corn popping in a popcorn machine. Interestingly, the CB1 receptor antagonist rimonabant stimulated locomotor activity in mice, suggesting that there is tonic activity in the endocannabinoid system that contributes to the control of spontaneous levels of activity (Compton et al., 1996).

These effects of cannabinoids may be due, in part, to actions at cerebellar or striatal receptors. Patel and Hillard (2001) used tests of specific cerebellar functions to show that cannabinoids caused increased gait width and the number of slips on a bar cross test. DeSanty and Dar (2001) observed rotorod impairments in mice after direct injection of synthetic cannabinoids into the cerebellum. These defects were no longer seen in animals pretreated with cerebellar injections of an antisense oligonucleotide directed to a sequence in the CB1 receptor.

In human subjects it is also possible to demonstrate that cannabis causes impaired performance in test of balance (Greenberg et al., 1994), or in tests that require fine psychomotor control, for example tracking a moving point of light on a screen (Manno et al., 1970). Human cannabis users may also seek isolation and remain immobile for long periods.

A number of authors have attempted to combine what is known of the neuroanatomical distribution of the cannabinoid system and the results of behavioural and electrophysiological studies to speculate on the mechanisms underlying cannabinoid modulation of psychomotor function (Breivogel and Childers, 1998; Sañudo-Peña et al., 1999; Giuffrida et al., 2000; Elphick and Egertová, 2001). The CB1 receptor is expressed particularly by striatal GABAergic medium-spiny projection neurons, and is abundant in regions containing the axon terminals of these cells (globus pallidus, entopeduncular nucleus and substantia nigra reticulata, and in axon collaterals feeding back to medium-spiny projection neurons in striatum). CB1 receptors are also abundant on the terminals of glutamatergic projection neurons from the subthalamic nucleus to globus pallidus, en-

topeduncular nucleus and substantia nigra reticulata. Cannabinoids might thus be expected to inhibit GABA release in striatum and GABA and glutamate release in the other nuclei. Sañudo-Peña et al. (1999) suggested that the primary role of the endocannabinoid system may be to inhibit tonic release of glutamate in the substantia nigra, regulating levels of basal motor activity. Exogenous cannabinoids also lead to decreased GABA release in substantia nigra, which could lead to a disinhibition of the inhibitory nigral input to the thalamocortical pathway, resulting in inhibition of movement. To what extent the effects of cannabinoids on motor function are due to actions in the cerebellum remains unclear, although as described above it is likely that effects on posture and balance are mediated in this brain region. As described previously, CB1 receptors are known to occur abundantly on nearly all of the principal excitatory (glutamatergic) and inhibitory (GABAergic) inputs to cerebellar Purkinje cells.

The results of eliminating the expression of CB1 receptors in knockout mice have yielded conflicting results. The knockout animals studied by Zimmer et al. (1999) displayed reduced levels of basal activity, in support of the hypothesis put forward by Sañudo-Peña et al. (1999), suggesting that tonic activation of CB1 receptors promotes movement. However, the CB1 knockout animals studied by Ledent et al. (1999) showed no change in spontaneous activity, and in some tests they exhibited increased motor activity. This is in line also with the observations of Compton et al. (1996) that the CB1 antagonist SR141716 caused an increase in locomotor activity. The reasons for the discrepant findings in different strains of CB1 knockout mice are unknown. Clearly, there is as yet only a poor understanding of the actions of cannabinoids in the basal ganglia and cerebellum. Interactions with other chemical signalling systems in the brain are likely to be important. Giuffrida et al. (1999) showed, for example, that dopamine D2 receptor agonists caused an increase in anandamide synthesis and release in striatum. Deadwyler et al. (1995) described the convergence of multiple presynaptic controls on the terminals of granule cells in cerebellum. In addition to the CB1 receptor, these terminals also express high densities of kappa opioid, adenosine A1 and GABA-B receptors, all of which are coupled through a similar Gi/o type G-protein to inhibit adenylate cyclase and are capable of inhibiting glutamate release. Such complexities are likely to prove the norm. There is anecdotal evidence that cannabis can relieve muscle pain and spasticity in patients suffering from multiple sclerosis (Consroe et al., 1996). Experimental data obtained by Baker et al. (2000) in an animal model of multiple sclerosis appears to support such claims. Mice immunized with myelin antigens develop spasticity and tremor. Both symptoms were ameliorated by administration of cannabinoids, and the symp-

toms were exacerbated by rimonabant, suggesting the involvement of CB1 receptors and tonic activity in the endocannabinoid system. Controlled clinical trials of cannabis-based medicines for the treatment of multiple sclerosis are currently under way.

Cannabinoid mechanisms in the hippocampus and effects on memory

One of the well established effects of acute intoxication with cannabis in man is an impairment of short-term memory (the extensive literature on human studies is reviewed by Jones, 1978; Miller and Branconnier, 1983; Solowij, 1998; Earleywine, 2002). Many studies have shown significant effects on short term memory, particularly when tests were used that depend heavily on attention (Abel, 1971; Mendelson et al., 1976). Animal studies have also found that THC, synthetic cannabinoids and anandamide cause deficits in short-term memory in spatial learning tasks (for a review see Hampson and Deadwyler, 1999). These include delayed matching or non-matching tests in rodents (Mallet and Beninger, 1998; Hampson and Deadwyler, 1999), performance in a radial arm maze (Stiglick and Kalant, 1985; Lichtman and Martin, 1996), and a fixed ratio food acquisition task in squirrel monkeys (Nakamura-Palacios et al., 2000). The effects of both cannabinoids (Lichtman and Martin, 1996) and anandamide (Mallet and Beninger, 1998) were reversed by rimonabant, indicating that they are mediated by the CB1 receptor.

A probable site for these effects is the hippocampus. Hampson and Deadwyler (1999) claimed that the effects of the treatment of rats with cannabinoids on short-term memory in a delayed non-matching to sample test were equivalent to the effects seen after surgical removal of the hippocampus. In each case the animals were unable to segregate information between trials in the task because of disruptions to the processing of sensory information in hippocampal circuits. CB1 receptors are expressed at high densities in the hippocampus. They are particularly abundant on the terminals of a sub-set of GABAergic basket cell interneurons, which also contain the neuropeptide cholecystinin (Katona et al., 1999), and this is also the case in human hippocampus (Katona et al., 2000). These are presumably the GABAergic neurons involved in the endocannabinoid-mediated DSI phenomenon described above. The terminals of these cells surround large pyramidal neuron somata in the CA1–CA4 fields. GABAergic neurons in the dentate gyrus also express CB1 receptors, with terminals concentrated at the boundary of the molecular and granule cell layers (Egertová and Elphick, 2000). In addition CB1 receptors are expressed, at a lower level, in the glutamatergic pyramidal cells and their terminals. Cannabinoids can thus inhibit both the release of GABA and glutamate in hippocampal circuits.

The mechanisms underlying synaptic plasticity have been studied more intensely in the hippocampus than in any other brain region. In particular, the electrophysiological phenomena of long-term potentiation (LTP) and long-term depression (LTD) are thought to be involved in memory formation at glutamatergic synapses in the hippocampus. A number of studies have shown clearly that cannabinoids inhibit the induction of both LTP and LTD (for review see Elphick and Egertová, 2001). Cannabinoids appear to work by reducing glutamate release below the level needed to activate NMDA receptors, a requirement for LTP and LTD (Shen et al., 1996; Misner and Sullivan, 1999). Although the actions of cannabinoids in reducing GABA release from hippocampal interneurons might have been expected to increase the level of excitability of hippocampal pyramidal cells, it seems that the cannabinoid-induced reduction in glutamate release predominates. The administration of exogenous cannabinoids is, of course, wholly unphysiological and cannot mimic the effects of endocannabinoids that are released in discrete local regions in response to particular patterns of afferent inputs. CB1 receptors are capable of regulating both inhibitory and excitatory neurotransmitter release in the hippocampus and are thus capable of subtle control of synaptic plasticity. The CB1-containing GABAergic interneurons are thought to control oscillatory electrical activity in the hippocampus in the theta and gamma frequencies, which plays a role in synchronizing pyramidal cell activity (Hoffman and Lupica, 2000). CB1 agonists decrease the power of such oscillations in hippocampal slices (Hájos et al., 2000) and may thus influence the synchronous activity of pyramidal cells. The physiological importance of cannabinoid-mediated DSI may be to decrease GABAergic inhibition of these cells and thus facilitate learning when hippocampal inputs are active (Wilson and Nicoll, 2001).

One approach to answering the question of what role the tonic release of endocannabinoids may play in hippocampal function has been to examine the effects of CB1 receptor knockout or of selective CB1 receptor antagonists. Unfortunately, these studies have so far yielded conflicting results. Bohme et al. (2000) reported a significant enhancement of LTP in CB1 knockout mice, and Reibaud et al. (1999) found a significant enhancement of memory in such animals. However, tests with the CB1 antagonist rimonabant showed no effects on LTP (Terranova et al., 1995) or on learning and memory in a spatial

learning task (Mallet and Beninger, 1998), although Terranova et al. (1996) reported that rimonabant enhanced memory in a short-term olfactory memory test in rats (social recognition test).

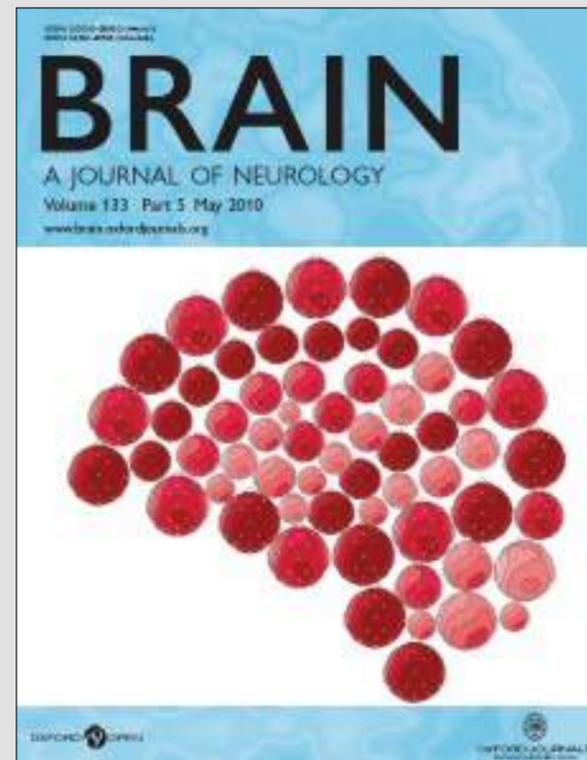
Cannabinoids and the neocortex

Like other intoxicant drugs cannabis causes profound changes in a variety of higher brain functions. The literature on the acute effects of the drug in human subjects is large, and can only be summarized here (for reviews see Jones, 1978; Solowij, 1998; Iversen, 2000; Earleywine, 2002). The distribution of CB1 receptors in the neocortex has been described in detail (Herkenham et al., 1991; Egertová and Elphick, 2000). As in the hippocampus, the majority of cortical interneurons expressing high levels of CB1 receptor are GABAergic cells, which also express cholecystokinin (Marsicano and Lutz, 1999). CB1-positive terminals are concentrated in layers II–III and layers V–VI, with few in layers I or IV. Despite the obvious importance of the abundant CB1 receptors in the neocortex there have so far been few electrophysiological studies of their effects on neural activity.

The earlier literature, however, contains several reports of the effects of acute and chronic cannabis use on EEG activity, both in man and animals (reviewed by Adams and Martin, 1996; Solowij, 1998). Most studies in man have observed changes consistent with a state of drowsiness, with increases in relative and absolute α power particularly in frontal regions of cortex. In contrast, the CB1 antagonist rimonabant was shown to induce EEG changes characteristic of

arousal in rats, and increased the time spent in wakefulness as opposed to sleep (Santucci et al., 1996). Mechoulam et al. (1997) have suggested that anandamide may play a role in the control of the sleep–waking cycle.

Studies of the effects of cannabis on perceptual abilities have yielded a variety of often conflicting results. While users often report a subjective enhancement of visual and auditory perception, sometimes with synesthesia (sounds take on visual colourful qualities), laboratory studies have usually not shown marked changes in visual or auditory perception. One subjective effect that has been confirmed is the sensation that cannabis users



experience time as passing more quickly relative to real time. In laboratory tests subjects overestimate the amount of elapsed time when asked to estimate, or produce shorter than required intervals when asked to signal a period of elapsed time (Hicks et al., 1984; Mathew et al., 1998). This curious effect can also be seen in rats trained to respond for food reward using a fixed interval schedule. When treated with THC or WIN55,2122 the animals shortened their response interval, whereas the antagonist rimonabant lengthened this interval (Han and Robinson, 2001).

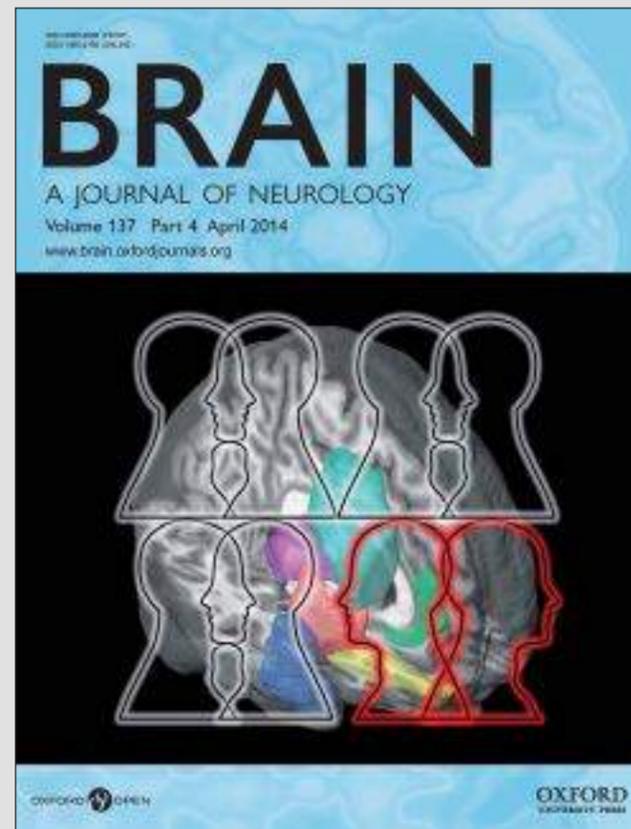
There have been many studies of the acute and chronic effects of cannabis on human cognitive function (Jones, 1978; Solowij, 1998; Earleywine, 2002). Performance on a variety of tests of cognitive function is impaired by the drug, but by comparison with alcohol the effects of cannabis are subtle. Whereas even moderate doses of alcohol, for example, impair reaction time, most studies with cannabis have failed to show consistent effects on measures of simple reaction time. Thus the drug's ability to disrupt cognitive function cannot be due to an inability to respond promptly. Among the impairments of cognitive function that have been observed in many, but not all, human studies are: decreased ability to inhibit responses, decreased vigilance, especially for long and boring tasks, decreased ability to perform complex mental arithmetic and impairments in tests of complex reaction times. On the other hand, intoxicated subjects can perform simple arithmetic, learn simple lists of words and recall memories laid down earlier.

Other studies have addressed the question of whether more severe deficits in cognitive function might develop in chronic heavy users of cannabis, or in animals treated for prolonged periods with the drug. The human studies are fraught with difficulties, as described in detail by Earleywine (2002). Among the confounding factors in human studies are that comparisons have to be made between groups of drug users versus non-users, but it is usually impossible to compare the baseline performance of these groups prior to cannabis use to see if they are properly matched. Statistical analysis of such data has often been poor, common errors being the use of so many different tests that the likelihood of finding some significant differences is increased, or the use of inadequate sample sizes. Other drug use can also confound the data. Results have been very variable. Some studies in long-term very heavy users of cannabis (10–20

joints per day for more than 10 years) in Jamaica (Bowman and Pihl, 1973) and Costa Rica (Satz et al., 1976) failed to show any significant difference between users versus non-users using a battery of test assessments of cognitive function, and similar negative results were reported in some studies of US college students (Earleywine, 2002). However, most reports have shown that there are deficits in the performance of complex cognitive tasks in long-term cannabis users, although there is little evidence that these are qualitatively or quantitatively more severe than those seen after acute use of the drug (Earleywine, 2002).

Even more controversial is the question of whether long-term cannabis use can cause irreversible deficits in higher brain function that persists after drug use stops. Many studies have suffered from poor design. It is not sufficient to identify a group of cannabis users and simply to test them after stopping cannabis use. Pope et al. (2001), for example, recruited 63 current heavy users, who had smoked cannabis at least 5000 times in their lives, and 72 control subjects. Subjects underwent a 28-day washout from cannabis use, monitored by urine assays. At days 0, 1 and 7 the heavy users scored significantly below control subjects on a battery of neuropsychological tests, particularly in recall of word lists. However, by day 28 there were virtually no differences between the groups on any of the test results, and no significant association between cumulative lifetime cannabis use and test scores. The fact that drug-induced effects on cognitive performance can persist for up to a week after stopping the drug (perhaps because of the persistence of THC in the body, or because of a subtle withdrawal syndrome)

means that many earlier studies that did not allow a sufficiently long washout period may be invalid. On the other hand, some well designed studies have shown subtle persistent cognitive deficits in ex-cannabis users. Solowij (1998) recruited a group of people who had used cannabis regularly for at least 5 years but who had stopped on average 2 years before the experiment. The subjects were given a very difficult task. They had to listen to a series of tones, some in the right ear some in the left; the tones were long or short (but differing by only 51 ms) and high or low pitch (but differing very little). Participants had to press a button as fast as possible in response to longer tones of a specified pitch in the correct ear. Previous research using this paradigm showed that current regular cannabis users had difficulty in discriminating between the tones. Mea-



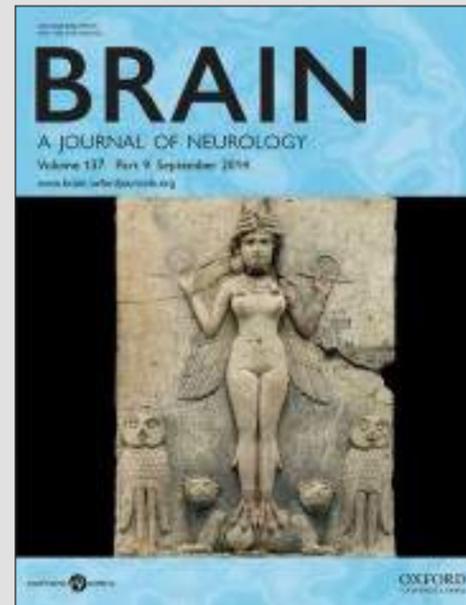
surements of event-related potentials also revealed small but significant abnormalities in the P300 wave (Solowij, 1998). The ex-users continued to make significant errors in the discrimination task, but they showed normal P300 waves. The conclusion of these and many other studies in ex-users seems to be that regular cannabis use can cause small but significant impairments in cognitive function that may persist after drug use stops. Such impairments appear to be associated with long-term heavy use of the drug and are unlikely to affect most recreational users.

Effects of cannabinoids on hypothalamic control of appetite

Many subjective reports suggest that cannabis intoxication is associated with an increased appetite, particularly for sweet foods, even in subjects who were previously satiated. This effect can be confirmed under laboratory conditions (Hollister, 1971; Mattes et al., 1994), although results from studies in human subjects have tended to be variable, perhaps because the increased appetite is focused on certain types of food. Nevertheless, controlled clinical trials showed that THC (dronabinol) had significant beneficial effects in counteracting the loss of appetite and reduction in body weight in patients suffering from the AIDS-related wasting syndrome (Beal et al., 1995), and this is one of the medical indications for which the drug has official approval in the USA.

THC also stimulates food intake in experimental animals, and again the effect is specific for high-fat or sweet high fat diets, and is not seen in animals offered standard rat chow (Koch, 2001). The endocannabinoid anandamide also stimulates food intake in rats, and the effect is blocked by rimonabant (Williams and Kirkham, 1999). Conversely the CB1 antagonist rimonabant given on its own suppressed food intake and led to reduced body weight in adult non-obese rats (Colombo et al., 1998). These results suggest that cannabinoids may play a role in the regulation of food intake and body weight (Mechoulam and Fride, 2001). A possible reciprocal link between endocannabinoid mechanisms and the appetite-suppressing hormone leptin was suggested by Di Marzo et al. (2001a). They found that food-deprived CB1 receptor knockout mice eat less than their wild-type litter mates, and the CB1 antagonist rimonabant reduced food intake in the wild-type animals but not in the knockouts. Animals with defective leptin signalling (obese db/db or ob/ob mice and Zucker rats) exhibited elevated hypothalamic levels of anandamide and 2-AG. On the other hand,

treatment of normal rats or ob/ob (leptin deficient) mice with leptin caused decreases in hypothalamic levels of the endocannabinoids. These findings suggest that hypothalamic endocannabinoids may play an important role in mediating the appetite-suppressant effects of leptin. At some stages during development these effects of endocannabinoids may be of critical importance. Fride et al. (2001) found that administration of the CB1 antagonist rimonabant to new-born mouse pups had a devastating effect in decreasing milk ingestion and growth, continuing treatment with the antagonist led to death within 4–8 days. The effect of rimonabant could be almost fully reversed by co-administering THC.



Cannabinoids as anti-emetic agents

The ability of THC and the synthetic cannabinoid nabilone to control the nausea and vomiting associated with cancer chemotherapy is one of the few well documented medical applications for these drugs (for reviews of the controlled clinical trials see Vincent et al., 1983; British Medical Association, 1997; Joy et al., 1999; and the meta-analysis reported by Tramèr et al., 2001). THC (dronabinol) and nabilone were approved for medical use in the USA, although neither drug has found much utility. The narrow window between the anti-emetic dose and that causing unwanted psychic effects made these drugs difficult to use. The advent of serotonin 5-HT₃ receptor antagonists as new and more powerful anti-emetic drugs that were free of unwanted psychic effects during the 1980s also made the cannabinoids less attractive.

Studies in experimental animals have confirmed that the anti-emetic effects of cannabinoids are mediated through CB1 receptors (Darmani, 2002), and in some susceptible species (e.g. the least shrew) the CB1 antagonist rimonabant is emetic, an effect that can be blocked by THC or WIN55,2122 (Darmani, 2001).

Cannabinoids and pain

Cannabis was widely used in 19th century medicine for pain relief and there is renewed interest in cannabis-based medicines, with pain as one of the key therapeutic targets (British Medical Association, 1997; Joy et al., 1999). Endogenous cannabinoids and cannabinoid receptors exist at various levels in the pain pathways, from peripheral sensory

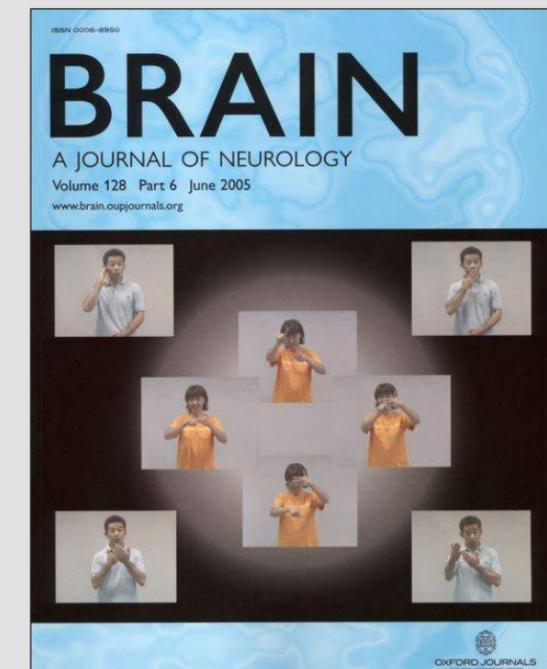
nerve endings to spinal cord and supraspinal centres, in a system that is parallel to but distinct from that involving endorphins and opiate receptors.

Systemically administered THC and synthetic cannabinoids have anti-nociceptive and anti-hyperalgesic effects in a variety of animal models of acute and inflammatory pain (for reviews see Pertwee, 2001; Iversen and Chapman, 2002). Since cannabinoids inhibit motor activity this could prevent animals from exhibiting the normal behavioural reactions in analgesic tests; however, a number of studies have also shown that cannabinoids suppress electrophysiological responses of spinal cord neurons to noxious stimulation, and block spinal c-fos expression in response to such stimulation (Walker et al., 1999; Pertwee, 2001; Iversen and Chapman, 2002). Cannabinoids and anandamide also exert anti-nociceptive effects in animal models of inflammatory pain when injected directly into spinal cord, brain stem or thalamus (Pertwee, 2001). Behavioural studies have shown that cannabinoids reduce thermal and mechanical allodynia in rat models of neuropathic pain (Herzberg et al., 1997; Fox et al., 2001; Iversen and Chapman, 2002). Furthermore, noxious stimulation evoked an increased release of anandamide in the periaqueductal grey region of brainstem, a key site for modulating nociceptive information (Walker et al., 1999). The anti-nociceptive effects of cannabinoids are blocked by the CB1 antagonist rimonabant, but the antagonist itself does not alter basal pain thresholds, suggesting that these are not controlled by tonic activity in the endocannabinoid system (Compton et al., 1996).

Results obtained with CB1 receptor knockout mice, however, suggest that not all of the anti-nociceptive effects of THC or anandamide are mediated via CB1 receptors. Thus, although Di Marzo et al. (2000) found that the anti-nociceptive effects of THC were virtually absent in the knockout animals, anandamide continued to show analgesic activity in the hot-plate test. It is possible that the analgesic effects of anandamide are mediated in part through an action at other as yet ill-defined cannabinoid receptors (Breivogel et al., 2001; Hájos et al., 2001). Alternatively, it has been proposed that the effects of anandamide might be mediated through its ability to bind to the vanilloid VR1 receptor, which is present in primary afferent neurons and known to play an important role in nociceptive responses (Di Marzo et al., 2001b). To complicate matters further, Zimmer et al. (1999), in a different strain of CB1 receptor knockout mice, found that THC continued to exert some anti-nociceptive actions in hot-plate and formalin tests in the knockout animals. The reasons for the discrepant results obtained with different strains of CB1 receptor knockout mice are unknown.

There is evidence for an interaction between cannabinoid and opioid mechanisms. In tests of acute pain (Fuentes et al., 1999) and chronic inflammatory pain (Welch and Stevens, 1992; Smith et al., 1998) THC and morphine acted synergically—one potentiated the anti-nociceptive actions of the other. This potentiation could be blocked by either rimonabant or by naloxone, indicating that both CB1 and opiate receptors were involved (Fuentes et al., 1999). Meng et al. (1998) showed that temporary inactivation of neural activity in the rostral ventromedial medulla (RVM) in rat brainstem prevented the analgesic effects of systemically administered cannabinoids, while leaving their effects on motor activity unaffected. An electrophysiological analysis of the effects of cannabinoids on single cell firing patterns in RVM revealed that the effects of cannabinoids were similar to those elicited by morphine. The authors concluded that cannabinoids may produce analgesia through activation of a brainstem circuit that is also required for opiate analgesia, although the two mechanisms are pharmacologically distinct.

Basic research into the role of cannabinoids and endocannabinoids in pain mechanisms is progressing rapidly. Clinical progress, however, has been slow. A meta-analysis of clinical trials of cannabinoids as analgesics concluded that there was not enough evidence to justify their use in this indication (Campbell et al., 2001). However, this may merely reflect the paucity of data from adequately sized controlled clinical trials, and cannabis-based medicines may yet find genuine medical applications in this field.



Full text with 168 references and a Must Read report

<http://brain.oxfordjournals.org/content/126/6/1252.long>

Early-onset cannabis use and cognitive deficits: what is the nature of the association?

Pope HG Jr¹, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D.

1. Department of Psychiatry, Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA
pope@mclean.harvard.edu

<http://www.ncbi.nlm.nih.gov/pubmed/12633916>

Individuals who initiate cannabis use at an early age, when the brain is still developing, might be more vulnerable to lasting neuropsychological deficits than individuals who begin use later in life.

We analyzed neuropsychological test results from 122 long-term heavy cannabis users and 87 comparison subjects with minimal cannabis exposure, all of whom had undergone a 28-day period of abstinence from cannabis, monitored by daily or every-other-day observed urine samples. We compared early-onset cannabis users with late-onset users and with controls, using linear regression controlling for age, sex, ethnicity, and attributes of family of origin.

The 69 early-onset users (who began smoking before age 17) differed significantly from both the 53 late-onset users (who began smoking at age 17 or later) and from the 87 controls on several measures, most notably verbal IQ (VIQ). Few differences were found between late-onset users and controls on the test battery. However, when we adjusted for VIQ, virtually all differences between early-onset users and controls on test measures ceased to be significant.

Early-onset cannabis users exhibit poorer cognitive performance than late-onset users or control subjects, especially in VIQ, but the cause of this difference cannot be determined from our data. The difference may reflect (1). innate differences between groups in cognitive ability, antedating first cannabis use; (2). an actual neurotoxic effect of cannabis on the developing brain; or (3). poorer learning of conventional cognitive skills by young cannabis users who have eschewed academics and diverged from the mainstream culture.

Journal Of Cellular Biochemistry • February 2003

Prospects for cannabinoids as anti-inflammatory agents

By R.B. Zurier

1. Department of Medicine, Division of Rheumatology, University of Massachusetts Medical School, Worcester, USA
robert.zurier@umassmed.edu

<http://www.ncbi.nlm.nih.gov/pubmed/12532323>

The marijuana plant (*Cannabis sativa*) and preparations derived from it have been used for medicinal purposes for thousands of years. It is likely that the therapeutic benefits of smoked marijuana are due to some combination of its more than 60 cannabinoids and 200-250 non-cannabinoid constituents. Several marijuana constituents, the carboxylic acid metabolites of tetrahydrocannabinol, and synthetic analogs are free of cannabimimetic central nervous system activity, do not produce behavioral changes in humans, and are effective antiinflammatory and analgesic agents. One cannabinoid acid in particular, ajulemic acid, has been studied extensively in in vitro systems and animal models of inflammation and immune responses. This commentary reviews a portion of the work done by investigators interested in separating the medicinal properties of marijuana from its psychoactive effects. Understanding the mechanisms of the therapeutic effects of nonpsychoactive cannabinoids should lead to development of safe effective treatment for several diseases, and may render moot the debate about "medical marijuana".

Journal Of Clinical Pharmacology • November 2002

**Adolescents prenatally exposed to marijuana:
examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes**

By P.A. Fried

Department of Psychology, Carleton University, Ottawa, Ontario, Canada

<http://www.ncbi.nlm.nih.gov/pubmed/12412842>

For the purposes of this review, the impact of prenatal exposure to marijuana in adolescent offspring is discussed in the context that the effects may be apparent only when the multifaceted nature of complex behaviors is examined and that such exposure can be distinguished from those of prenatal exposure to cigarettes. The data are derived from adolescents participating in an on going longitudinal study for whom prenatal marijuana and cigarette exposure had been ascertained with the low-risk, predominantly middle-class sample that had been assessed since birth. In this report, cognitive functioning and visual perceptual performance in 9- to 12-year-olds and facets of attention in 13- to 16-year-olds are examined. These three areas of behavior all appear to be affected differentially by maternal use of marijuana or cigarettes. Prenatal cigarette exposure was associated with lowered IQ, poorer impulse control, and poorer performance on tests requiring fundamental aspects of visuoperceptual performance. In contrast, prenatal marijuana did not have a negative impact on IQ or on basic visuoperceptual skills. Rather, in utero exposure to marijuana had an impact on the application of these skills in tasks in problem-solving situations requiring visual integration and analytical skills as well as sustained attention. These differential findings are discussed in terms of cigarette exposure having a "bottom-up" impact and marijuana exposure having a "top-down" impact. The latter is also discussed in terms of prenatal marijuana's negative association with aspects of executive function.

Respiratory and immunologic consequences of marijuana smoking

Tashkin DP1, Baldwin GC, Sarafian T, Dubinett S, Roth MD.

Department of Medicine, UCLA School of Medicine, 90095-1690, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412839>

Habitual smoking of marijuana has a number of effects on the respiratory and immune systems that may be clinically relevant. These include alterations in lung function ranging from no to mild airflow obstruction without evidence of diffusion impairment, an increased prevalence of acute and chronic bronchitis, striking endoscopic findings of airway injury (erythema, edema, and increased secretions) that correlate with histopathological alterations in bronchial biopsies, and dysregulated growth of the bronchial epithelium associated with altered expression of nuclear and cytoplasmic proteins involved in the pathogenesis of bronchogenic carcinoma. Other consequences of regular marijuana use include ultrastructural abnormalities in human alveolar macrophages along with impairment of their cytokine production, antimicrobial activity, and tumoricidal function. Cannabinoid receptor expression is altered in leukocytes collected from the blood of chronic smokers, and experimental models support a role for delta9-tetrahydrocannabinol in suppressing T cell function and cell-mediated immunity. The potential for marijuana smoking to predispose to the development of respiratory malignancy is suggested by several lines of evidence, including the presence of potent carcinogens in marijuana smoke and their resulting deposition in the lung, the occurrence of premalignant changes in bronchial biopsies obtained from smokers of marijuana in the absence of tobacco, impairment of antitumor immune defenses by delta9-tetrahydrocannabinol, and several clinical case series in which marijuana smokers were disproportionately over represented among young individuals who developed upper or lower respiratory tract cancer. Additional well designed epidemiological and immune monitoring studies are required to determine the potential causal relationship between marijuana use and the development of respiratory infection and/or cancer.

Marijuana smoking and head and neck cancer

Hashibe M1, Ford DE, Zhang ZF.

Department of Epidemiology, UCLA School of Public Health, Jonsson Comprehensive Cancer Center, 90095-1772, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412843>

A recent epidemiological study showed that marijuana smoking was associated with an increased risk of head and neck cancer. Among high school students and young adults, the prevalence of marijuana use was on the rise in the 1990s, with a simultaneous decline in the perception that marijuana use is harmful. It will be a major public health challenge to make people aware of the harmful effects of marijuana smoking, when some people view it as the illicit drug with the least risk. The carcinogenicity of delta9-tetrahydrocannabinol (THC) is not clear, but according to laboratory studies, it appears to have antitumor properties such as apoptosis as well as tumor-promoting properties such as limiting immune function and increasing reactive oxygen species. Marijuana tar contains similar carcinogens to tar from tobacco cigarettes, but each marijuana cigarette may be more harmful than a tobacco cigarette since more tar is inhaled and retained when smoking marijuana. More molecular alterations have been observed in bronchial mucosa specimens of marijuana smokers compared to nonsmokers. Field cancerization may be occurring on the bronchial epithelium due to marijuana smoking exposure. Several case studies were suggestive of an association of marijuana smoking with head and neck cancers and oral lesions. However, in a cohort study with 8 years of follow-up, marijuana use was not associated with increased risks of all cancers or smoking-related cancers. Further epidemiological studies are necessary to confirm the association of marijuana smoking with head and neck cancers and to examine marijuana smoking as a risk factor for lung cancer. It will also be of interest to examine potential field cancerization of the upper aerodigestive tract by marijuana and to explore marijuana as a risk factor for oral premalignant lesions.

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Endocrine effects of marijuana

Brown TT1, Dobs AS.

Division of Endocrinology and Metabolism, Johns Hopkins University, Baltimore, Maryland 21287, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412841>

In the 35 years since the active compound of marijuana, delta9-tetrahydrocannabinol, was isolated, the psychological and physiological impact of marijuana use has been actively investigated. Animal models have demonstrated that cannabinoid administration acutely alters multiple hormonal systems, including the suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and the activation of the hypothalamic-pituitary-adrenal axis. These effects are mediated by binding to the endogenous cannabinoid receptor in or near the hypothalamus. Despite these findings in animals, the effects in humans have been inconsistent, and discrepancies are likely due in part to the development of tolerance. The long-term consequences of marijuana use in humans on endocrine systems remain unclear.

Journal Of Clinical Pharmacology • November 2002

**Adolescents prenatally exposed to marijuana:
examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes**

By P.A. Fried

Department of Psychology, Carleton University, Ottawa, Ontario, Canada

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For the purposes of this review, the impact of prenatal exposure to marijuana in adolescent offspring is discussed in the context that the effects may be apparent only when the multifaceted nature of complex behaviors is examined and that such exposure can be distinguished from those of prenatal exposure to cigarettes. The data are derived from adolescents participating in an on going longitudinal study for whom prenatal marijuana and cigarette exposure had been ascertained with the low-risk, predominantly middle-class sample that had been assessed since birth. In this report, cognitive functioning and visual perceptual performance in 9- to 12-year-olds and facets of attention in 13- to 16-year-olds are examined. These three areas of behavior all appear to be affected differentially by maternal use of marijuana or cigarettes. Prenatal cigarette exposure was associated with lowered IQ, poorer impulse control, and poorer performance on tests requiring fundamental aspects of visuoperceptual performance. In contrast, prenatal marijuana did not have a negative impact on IQ or on basic visuoperceptual skills. Rather, in utero exposure to marijuana had an impact on the application of these skills in tasks in problem-solving situations requiring visual integration and analytical skills as well as sustained attention. These differential findings are discussed in terms of cigarette exposure having a "bottom-up" impact and marijuana exposure having a "top-down" impact. The latter is also discussed in terms of prenatal marijuana's negative association with aspects of executive function.

Cardiovascular consequences of marijuana use

By S. Sidney

Kaiser Permanente Medical Care Program, Division of Research, Oakland, California 94612, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412838>

This review describes what is known about effects of marijuana and cannabinoids in relation to human physiological and disease outcomes. The acute physiological effects of marijuana include a substantial dose-dependent increase in heart rate, generally associated with a mild increase in blood pressure. Orthostatic hypotension may occur acutely as a result of decreased vascular resistance. Smoking marijuana decreases exercise test duration in maximal exercise tests, increases the heart rate at submaximal levels of exercise. Tolerance develops to the acute effects of marijuana smoking and delta9-tetrahydrocannabinol (THC) over several days to a few weeks. The cardiovascular responses that occur in response to THC are mediated by the autonomic nervous system, with recent findings also demonstrating that the human cannabinoid receptor system plays a role in regulating the cardiovascular response. Although several mechanisms exist by which marijuana use might contribute to the development of chronic cardiovascular conditions or acutely trigger cardiovascular events, there are few data regarding marijuana/THC use and cardiovascular disease outcomes. A large cohort study showed no association of marijuana use with cardiovascular disease hospitalization or mortality. However, acute effects of marijuana use include a decrease of the time until the onset of chest pain in patients with angina pectoris; one study has shown that marijuana may trigger the onset of myocardial infarction. Patients who have coronary heart disease or are at high risk for the development of CHD should be cautioned about the potential hazards of marijuana use as a precipitant for clinical events. Research directions might include more studies of cardiovascular disease outcomes and relationships of marijuana with cardiovascular risk factors, studies of metabolic and physiologic effects of chronic marijuana use that may affect cardiovascular disease risk, increased understanding of the role of the cannabinoid receptor system in cardiovascular regulation, and studies to determine if there is a therapeutic role for cannabinoids in blood pressure control or for neuroprotection after stroke.

Journal Of Clinical Pharmacology • November 2002

Cardiovascular system effects of marijuana

By R.T. Jones.

Langley Porter Psychiatric Institute, Department of Psychiatry, University of California, San Francisco 94143-0984, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412837>

Marijuana and delta9-tetrahydrocannabinol (THC) increase heart rate, slightly increase supine blood pressure, and on occasion produce marked orthostatic hypotension. Cardiovascular effects in animals are different, with bradycardia and hypotension the most typical response. Cardiac output increases, and peripheral vascular resistance and maximum exercise performance decrease. Tolerance to most of the initial cardiovascular effects appears rapidly. With repeated exposure, supine blood pressure decreases slightly, orthostatic hypotension disappears, blood volume increases, heart rate slows, and circulatory responses to exercise and Valsalva maneuver are diminished, consistent with centrally mediated, reduced sympathetic, and enhanced parasympathetic activity. Receptor-mediated and probably nonneuronal sites of action account for cannabinoid effects. The endocannabinoid system appears important in the modulation of many vascular functions. Marijuana's cardiovascular effects are not associated with serious health problems for most young, healthy users, although occasional myocardial infarction, stroke, and other adverse cardiovascular events are reported. Marijuana smoking by people with cardiovascular disease poses health risks because of the consequences of the resulting increased cardiac work, increased catecholamine levels, carboxyhemoglobin, and postural hypotension.

Journal Of Clinical Pharmacology • November 2002

Cognitive measures in long-term cannabis users

Pope HG Jr¹, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D.

Biological Psychiatry Laboratory, McLean Hospital/Harvard Medical School, Belmont, Massachusetts 02478, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412835>

The cognitive effects of long-term cannabis use are insufficiently understood. Most studies concur that cognitive deficits persist at least several days after stopping heavy cannabis use. But studies differ on whether such deficits persist long term or whether they are correlated with increasing duration of lifetime cannabis use. The authors administered neuropsychological tests to 77 current heavy cannabis users who had smoked cannabis at least 5000 times in their lives, and to 87 control subjects who had smoked no more than 50 times in their lives. The heavy smokers showed deficits on memory of word lists on Days 0, 1, and 7 of a supervised abstinence period. By Day 28, however, few significant differences were found between users and controls on the test measures, and there were few significant associations between total lifetime cannabis consumption and test performance. Although these findings may be affected by residual confounding, as in all retrospective studies, they suggest that cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use.

Effects of smoked marijuana in healthy and HIV + marijuana smokers

By M. Haney

New York State Psychiatric Institute, Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York 10032, USA

<http://www.ncbi.nlm.nih.gov/pubmed/12412834>

This article presents data from two avenues of marijuana research. First, the author shows that daily marijuana smoking in healthy individuals produces dependence, as demonstrated by withdrawal symptoms such as increased irritability and depression and decreased food intake. In addition, two antidepressant medications were evaluated to assess their potential effectiveness in the treatment of marijuana withdrawal symptoms: (1) sustained-release bupropion (0, 300 mg/day) and (2) nefazodone (0, 450 mg/day). Research participants were regular marijuana smokers who lived in a residential laboratory in groups of two to four. While inpatients, participants smoked active marijuana (2.8%-3.1% THC) repeatedly for 4 days, followed by 8 to 12 days of placebo marijuana (0.0% THC). Results show that during marijuana abstinence, (1) bupropion increased ratings of irritability, depression, and stomach pain and decreased food intake and sleep quality compared to placebo maintenance, and (2) nefazodone decreased anxiety during marijuana withdrawal but did not alter ratings of irritability and misery. Thus, neither medication showed promise as potential treatments for symptoms of marijuana withdrawal. The second avenue of research focused on the effect of cannabinoids in individuals with muscle mass loss, an indicator of wasting in HIV illness. Given that there are little scientific data contributing to the debates concerning medical marijuana, this study directly compared the effects of oral delta9-THC (0, 10, 20, 30 mg PO) to smoked marijuana (0.0%, 1.8%, 2.8%, 3.9% THC) in HIV + marijuana smokers with muscle mass loss (< 90% body cell mass/height). Multiple dimensions of human behavior were measured, including food intake, mood, and cognitive performance. Drugs were administered using a within-subject, double-blind, staggered, double-dummy design. Participants were free to self-select from a variety of foods throughout most of the session. Preliminary data (n = 9) suggest that oral THC was more effective at increasing food intake, but the volunteers "liked" the effects of smoked marijuana more than the effects of oral THC.

Pharmacology & Therapeutics • August 2002

Tetrahydrocannabinol and endocannabinoids in feeding and appetite

Berry EM1, Mechoulam R.

1. Department of Human Nutrition and Metabolism, Hebrew University, School of Public Health and Faculty of Medicine, Jerusalem 91120, Israel

<http://www.ncbi.nlm.nih.gov/pubmed/12182965>

The physiological control of appetite and satiety, in which numerous neurotransmitters and neuropeptides play a role, is extremely complex. Here we describe the involvement of endocannabinoids in these processes. These endogenous neuromodulators enhance appetite in animals. The same effect is observed in animals and in humans with the psychotropic plant cannabinoid Delta(9)-tetrahydrocannabinol, which is an approved appetite-enhancing drug. The CB(1) cannabinoid receptor antagonist SR141716A blocks the effects on feeding produced by the endocannabinoids. If administered to mice pups, this antagonist blocks suckling. In obese humans, it causes weight reduction. Very little is known about the physiological and biochemical mechanisms involved in the effects of Delta(9)-tetrahydrocannabinol and the cannabinoids in feeding and appetite.

Pharmacology & Therapeutics • August 2002

Cannabinoids and multiple sclerosis

By R.G. Pertwee

Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Scotland, UK
rgp@aberdeen.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/12182963>

There is a growing amount of evidence to suggest that cannabis and individual cannabinoids may be effective in suppressing certain symptoms of multiple sclerosis and spinal cord injury, including spasticity and pain. Anecdotal evidence is to be found in newspaper reports and also in responses to questionnaires. Clinical evidence comes from trials, albeit with rather small numbers of patients. These trials have shown that cannabis, Delta(9)-tetrahydrocannabinol, and nabilone can produce objective and/or subjective relief from spasticity, pain, tremor, and nocturia in patients with multiple sclerosis (8 trials) or spinal cord injury (1 trial). The clinical evidence is supported by results from experiments with animal models of multiple sclerosis. Some of these experiments, performed with mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), have provided strong evidence that cannabinoid-induced reductions in tremor and spasticity are mediated by cannabinoid receptors, both CB(1) and CB(2). Endocannabinoid concentrations are elevated in the brains and spinal cords of CREAE mice with spasticity, and in line with this observation, spasticity exhibited by CREAE mice can be ameliorated by inhibitors of endocannabinoid membrane transport or enzymic hydrolysis. Research is now needed to establish whether increased endocannabinoid production occurs in multiple sclerosis. Future research should also be directed at obtaining more conclusive evidence about the efficacy of cannabis or individual cannabinoids against the signs and symptoms of these disorders, at devising better modes of administration for cannabinoids and at exploring strategies that maximize separation between the sought-after therapeutic effects and the unwanted effects of these drugs.

The pharmacology of cannabinoid derivatives: are there applications to treatment of pain?

Beaulieu P1, Rice AS.

Département d'anesthésiologie, CHUM, Hôtel-Dieu, 3840 Saint-Urbain, Montréal, Québec, Canada
pierre.beaulieu@umontreal.ca

<http://www.ncbi.nlm.nih.gov/pubmed/12134594>

Recent advances have dramatically increased our understanding of cannabinoid pharmacology. The psychoactive constituents of *Cannabis sativa* have been isolated, synthetic cannabinoids described and an endocannabinoid system identified, together with its component receptors and ligands. Strong laboratory evidence now underwrites anecdotal claims of cannabinoid analgesia in inflammatory and neuropathic pain. Sites of analgesic action have been identified in brain, spinal cord and the periphery, with the latter two presenting attractive targets for divorcing the analgesic and psychotropic effects of cannabinoids. Clinical trials are now required, but are hindered by a paucity of cannabinoids of suitable bioavailability and therapeutic ratio.

The cannabinoid system is a major target in the treatment of pain and its therapeutic potential should be assessed in the near future by the performance of new clinical trials.

Oral cytology in cannabis smokers

Darling MR1, Learmonth GM, Arendorf TM.

1. Department of Diagnostic Sciences, Division of Oral Pathology, School of Dentistry, Faculty of Health Sciences, University of Stellenbosch

<http://www.ncbi.nlm.nih.gov/pubmed/12078330>

The effects of cannabis/methaqualone/tobacco smoking on the epithelial cells of the tongue, buccal mucosa and floor of the mouth were examined. Oral mucosal smears for detection of cellular changes were taken from 4 sites in 16 patients. The tongue blade scraping technique was used. The sites sampled included the buccal mucosa (left and right sides), the posterior dorsum of the tongue and the anterior floor of the mouth. Tobacco smoking and non-smoking controls were also examined. The only significant difference between cannabis users and controls was the greater prevalence of bacterial cells in the smears taken from cannabis users. However, there were also greater numbers of degenerate and atypical squamous cells in cannabis smokers than in cigarette-smoking and non-smoking controls. Epithelial cells in smears taken from cannabis users and tobacco-smoking controls also showed koilocytic changes, which were not seen in smears taken from non-smoking controls. Koilocytosis is indicative of human papilloma virus infection, although no apparent lesions were seen in the patients from whom smears had been taken. It would appear that there is a greater tendency towards damaged and immature surface epithelial cells in cannabis smokers.

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Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults

Fried P1, Watkinson B, James D, Gray R.

Department of Psychology, Carleton University, Ottawa, Ontario, Canada
peter_fried@carleton.ca

Full text with 34 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC100921/>

Assessing marijuana's impact on intelligence quotient (IQ) has been hampered by a lack of evaluation of subjects before they begin to use this substance. Using data from a group of young people whom we have been following since birth, we examined IQ scores before, during and after cessation of regular marijuana use to determine any impact of the drug on this measure of cognitive function.

Current marijuana use was significantly correlated ($p < 0.05$) in a dose-related fashion with a decline in IQ over the ages studied. The comparison of the IQ difference scores showed an average decrease of 4.1 points in current heavy users ($p < 0.05$) compared to gains in IQ points for light current users (5.8), former users (3.5) and non-users (2.6).

Current marijuana use had a negative effect on global IQ score only in subjects who smoked 5 or more joints per week. A negative effect was not observed among subjects who had previously been heavy users but were no longer using the substance. We conclude that marijuana does not have a long-term negative impact on global intelligence. Whether the absence of a residual marijuana effect would also be evident in more specific cognitive domains such as memory and attention remains to be ascertained.

Cognitive functioning of long-term heavy cannabis users seeking treatment

Solowij N1, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J; Marijuana Treatment Project Research Group.

National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia
n.solowij@unsw.edu.au

<http://www.ncbi.nlm.nih.gov/pubmed/11879109>

Cognitive impairments are associated with long-term cannabis use, but the parameters of use that contribute to impairments and the nature and endurance of cognitive dysfunction remain uncertain.

Measures from 9 standard neuropsychological tests that assessed attention, memory, and executive functioning, and were administered prior to entry to a treatment program and following a median 17-hour abstinence.

Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. On the Rey Auditory Verbal Learning Test, long-term users recalled significantly fewer words than either shorter-term users ($P = .001$) or controls ($P = .005$); there was no difference between shorter-term users and controls. Long-term users showed impaired learning ($P = .007$), retention ($P = .003$), and retrieval ($P = .002$) compared with controls. Both user groups performed poorly on a time estimation task ($P < .001$ vs controls). Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use.

These results confirm that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

Anandamide receptors

Di Marzo V1, De Petrocellis L, Fezza F, Ligresti A, Bisogno T.

Endocannabinoid Research Group, Istituto di Chimica Biomdecolare, 80078 Pozzuoli, Naples, Italy
vdimarzo@icmib.na.cnr.it

<http://www.ncbi.nlm.nih.gov/pubmed/12052051>

Anandamide (N -arachidonoyl-ethanolamine, AEA) was the first endogenous ligand of cannabinoid receptors to be discovered. Yet, since early studies, AEA appeared to exhibit also some effects that were not mediated by cannabinoid CB(1) or CB(2) receptors. Indeed, AEA exerts some behavioral actions also in mice with genetically disrupted CB(1) receptors, whereas in vitro it is usually a partial agonist at these receptors and a weak activator of CB(2) receptors. Nevertheless, several pharmacological effects of AEA are mediated by CB(1) receptors, which, by being coupled to G-proteins, can be seen as AEA "metabotropic" receptors. Furthermore, at least two different, and as yet uncharacterized, G-protein-coupled AEA receptors have been suggested to exist in the brain and vascular endothelium, respectively. AEA is also capable of directly inhibiting ion currents mediated by L-type Ca(2+) channels and TASK-1 K(+) channels. However, to date the only reasonably well characterized, non-cannabinoid site of action for AEA is the vanilloid receptor type 1 (VR1), a non-selective cation channel gated also by capsaicin, protons and heat. VR1 might be considered as an AEA "ionotropic" receptor and, under certain conditions, mediates effects ranging from vasodilation, broncho-constriction, smooth muscle tone modulation and nociception to stimulation of hippocampal pair-pulse depression, inhibition of tumor cell growth and induction of apoptosis.

Cannabinoid receptors and their ligands

Pertwee RG1, Ross RA.

Department of Biomedical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK
rgp@aberdeen.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/12052030>

There are at least two types of cannabinoid receptors, CB(1) and CB(2), both coupled to G proteins. CB(1) receptors exist primarily on central and peripheral neurons, one of their functions being to modulate neurotransmitter release. CB(2) receptors are present mainly on immune cells. Their roles are proving more difficult to establish but seem to include the modulation of cytokine release. Endogenous agonists for cannabinoid receptors (endocannabinoids) have also been discovered, the most important being arachidonoyl ethanolamide (anandamide), 2-arachidonoyl glycerol and 2-arachidonoyl glyceryl ether. Other endocannabinoids and cannabinoid receptor types may also exist. Although anandamide can act through CB(1) and CB(2) receptors, it is also a vanilloid receptor agonist and some of its metabolites may possess yet other important modes of action. The discovery of the system of cannabinoid receptors and endocannabinoids that constitutes the "endocannabinoid system" has prompted the development of CB(1)- and CB(2)-selective agonists and antagonists/inverse agonists. CB(1)/CB(2) agonists are already used clinically, as anti-emetics or to stimulate appetite. Potential therapeutic uses of cannabinoid receptor agonists include the management of multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, vasodilation that accompanies advanced cirrhosis, and cancer. Following their release onto cannabinoid receptors, endocannabinoids are removed from the extracellular space by membrane transport and then degraded by intracellular enzymic hydrolysis. Inhibitors of both these processes have been developed. Such inhibitors have therapeutic potential as animal data suggest that released endocannabinoids mediate reductions both in inflammatory pain and in the spasticity and tremor of multiple sclerosis. So too have CB(1) receptor antagonists, for example for the suppression of appetite and the management of cognitive dysfunction or schizophrenia.

Psychological Medicine • January 2002

Early adolescent marijuana use: risks for the transition to young adulthood

Brook JS1, Adams RE, Balka EB, Johnson E.

<http://www.ncbi.nlm.nih.gov/pubmed/11883732>

This study assessed the relationship of early adolescent marijuana use to performance of developmental tasks integral to the transition to young adulthood. The tasks concerned intimacy, education, and work and social conformity.

African American (N = 617) and Puerto Rican (N = 531) youths completed questionnaires in their classrooms. Five years later they were individually interviewed. Logistic regression analysis estimated the increased likelihood that early marijuana users would make an inadequate transition to young adult social roles.

Analyses examining the association between early marijuana use and 20 outcome variables found significant relationships for 10 of them: (a) having lower educational and occupational expectations; (b) being suspended or expelled from school, fired from jobs, 'high' at school or work, collecting welfare; and (c) rebelliousness, not participating in productive activities, not attending church, and being an unmarried parent. Marijuana use was not related to any of the intimate relationship measures. These findings emerged with controls on gender, ethnicity, age and mother's education.

Among African Americans and Puerto Ricans, early marijuana use predicts less adequate performance on some developmental tasks integral to becoming an independent young adult. Marijuana is not a benign drug and is associated with future risks for the individual and society at large.

Journal Of Child Psychology And Psychiatry • January 2002

**Conceptual issues in behavioral teratology
and their application in determining long-term sequelae of prenatal marihuana exposure**

By P.A. Fried

Department of Psychology, Carleton University, Ottawa, Ontario, Canada
peter_fried@carleton.ca

<http://www.ncbi.nlm.nih.gov/pubmed/11848338>

Behavioral teratology, particularly as it is applied to the evaluation of cognition and behavior of children beyond the toddler stage, has become an area of burgeoning activity. In the area of drug abuse, children exposed in utero are often at developmental peril because of non-drug pre- and postnatal risk factors that make a causal association between the drug of interest and a behavioral teratogenic outcome increasingly problematic as the child gets older.

The results and the interpretation of the prenatal marihuana findings are discussed in terms of the behavioral teratogenic effects (or lack of effects) during the various developmental stages of the offspring, the non-unitary nature of executive function, cannabis receptors, and the consequences of chronic marihuana use in the non-pregnant population.

Differential effects of delta 9-THC on spatial reference and working memory in mice

Varvel SA1, Hamm RJ, Martin BR, Lichtman AH.

1. Department of Pharmacology, VCU, Richmond, VA 23298, USA

<http://www.ncbi.nlm.nih.gov/pubmed/11594438>

Marijuana remains the most widely used illicit drug in the U.S., and recent attention has been given to putative therapeutic uses of marijuana and cannabinoid derivatives. Thus, developing a better understanding of delta9-THC (tetrahydrocannabinol)-induced mnemonic deficits is of critical importance.

These experiments were conducted to determine whether delta9-THC has differential effects on spatial reference and working memory tasks, to investigate its receptor mechanism of action, and to compare these effects with those produced by two other compounds--scopolamine and phencyclidine--known to produce mnemonic deficits. In addition, the potency of delta9-THC in these memory tasks was compared with its potency in other pharmacological effects traditionally associated with cannabinoid activity.

Two different versions of the Morris water maze were employed: a working memory task and a reference memory task. Other effects of delta9-THC were assessed using standard tests of hypomotility, antinociception, catalepsy, and hypothermia.

delta9-THC disrupted performance of the working memory task (3.0 mg/kg) at doses lower than those required to disrupt performance of the reference memory task (100 mg/kg), or elicit hypomotility, antinociception, catalepsy, and hypothermia. These performance deficits were reversed by SR 141716A. The effects of delta9-THC resembled those of scopolamine, which also selectively disrupted the working maze task. Conversely, phencyclidine disrupted both tasks only at a dose that also produced motor deficits.

These data indicate that delta9-THC selectively impairs performance of a working memory task through a CB1 receptor mechanism of action and that these memory disruptions are more sensitive than other pharmacological effects of delta9-THC.

Molecular Neurobiology • August 2001

Cannabinoids and neuroprotection

Grundy RI1, Rabuffetti M, Beltramo M.

Schering Plough Research Institute, Milan, Italy
robert.grundy@spcorp.com

<http://www.ncbi.nlm.nih.gov/pubmed/11831553>

Cannabinoid compounds are endowed with pharmacological properties that make them interesting candidates for therapeutic development. These properties have been known since antiquity. However, in the last decade extremely important advances in the understanding of the physiology, pharmacology, and molecular biology of the cannabinoid system have given this field of research fresh impetus and have renewed the interest in the possible clinical exploitation of these compounds. In the present review we summarize the effects elicited, at the cellular level, by cannabinoids acting through receptor-dependent and receptor-independent mechanisms. These data suggest different ways by which cannabinoids may act as neuroprotective agents (prevention of excitotoxicity by inhibition of glutamate release, antioxidant effects, anti-inflammatory actions, etc.). The experimental evidence supporting these hypotheses are presented and discussed with regard to both preclinical and clinical studies in disease states such as cerebral ischemia, brain trauma, and Multiple Sclerosis.

Marijuana: federal smoke clears, a little

[No authors listed]

Full text with 4 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC81049/>

Fourteen years after narcotics police arrested Terrance Parker (who had discovered that smoking marijuana reduced the frequency of his grand mal seizures), and a year after the Ontario Court of Appeal ruled that Canada's discretionary regulation of the medicinal use of marijuana was "unfettered and unstructured ... [and] not consistent" with the principles of fundamental justice,¹ our federal government has taken the bold little step of drafting new regulations.

In Canada, even the simple possession of small amounts of marijuana for personal use is a criminal offense, unless you are one of the roughly 40 Canadians who have obtained a special dispensation to use cannabis to relieve the symptoms of cancer, AIDS, multiple sclerosis or epilepsy. The program is unduly restrictive. The new regulations promise more transparency in the review of applications to grow or possess medicinal marijuana, a broader definition of medical necessity, and greater latitude for physicians in determining the needs of individual patients.

There are no persuasive randomized trials of marijuana therapy for the relief of symptoms such as pain and nausea. Such trials are extremely difficult to do. But the ratio of drug effect (however subjective that effect may be) to drug harm is large: there are no reported cases of fatal marijuana overdose. The risks of lung cancer (from the tars in the smoke) or the very weak (and perhaps nonexistent) risk of addiction are mostly irrelevant to patients with terminal disease or severe chronic conditions. About 400 000 Canadians use

cannabis for medical reasons.² Professional organizations such as the CMA must move quickly to issue guidelines for physicians who, increasingly, will be asked for advice by their patients.

Health Canada's decision to legitimize the medicinal use of marijuana is a step in the right direction. But a bolder stride is needed. The possession of small quantities for personal use should be decriminalized. The minimal negative health effects of moderate use³ would be attested to by the estimated 1.5 million Canadians who smoke marijuana for recreational purposes.² The real harm is the legal and social fallout. About half of all drug arrests in Canada are for simple possession of small amounts of marijuana: about 31 299 convictions in 1995 alone.⁴ Many lead to jail terms or fines and all result in that indelible social tattoo: a criminal record. This means that for anyone who's ever been caught with a stash in his or her pocket, the question "Have you ever had a criminal conviction?" during a job application or medical school interview can force higher aspirations to go up in a puff of smoke.

The decriminalization of marijuana possession for personal use does not mean making marijuana "legal" or letting it be sold in every schoolyard. It does mean that possession of small amounts for personal use would become a civil offense, like a traffic violation, not a criminal one. The provisions of Canada's Contraventions Act make this a relatively simple legislative task. Mr. Justice Minister, let's decriminalize the possession of small amounts of marijuana for personal use.

The neurobiology and evolution of cannabinoid signalling

Elphick MR1, Egertová M.

School of Biological Sciences, Queen Mary, University of London, London E1 4NS, UK
m.r.elphick@qmw.ac.uk

Full text PDF with 100 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1088434/pdf/TB010381.pdf>

The plant *Cannabis sativa* has been used by humans for thousands of years because of its psychoactivity. The major psychoactive ingredient of cannabis is Delta(9)-tetrahydrocannabinol, which exerts effects in the brain by binding to a G-protein-coupled receptor known as the CB1 cannabinoid receptor. The discovery of this receptor indicated that endogenous cannabinoids may occur in the brain, which act as physiological ligands for CB1. Two putative endocannabinoid ligands, arachidonylethanolamide ('anandamide') and 2-arachidonylglycerol, have been identified, giving rise to the concept of a cannabinoid signalling system. Little is known about how or where these compounds are synthesized in the brain and how this relates to CB1 expression. However, detailed neuroanatomical and electrophysiological analysis of mammalian nervous systems has revealed that the CB1 receptor is targeted to the presynaptic terminals of neurons where it acts to inhibit release of 'classical' neurotransmitters. Moreover, an enzyme that inactivates endocannabinoids, fatty acid amide hydrolase, appears to be preferentially targeted to the somatodendritic compartment of neurons that are postsynaptic to CB1-expressing axon terminals. Based on these findings, we present here a model of cannabinoid signalling in which anandamide is synthesized by postsynaptic cells and acts as a retrograde messenger molecule to modulate neurotransmitter release from presynaptic terminals. Using this model as a framework, we discuss the role of cannabinoid signalling in different regions of the nervous system in relation to the characteristic physiological actions of cannabinoids in mammals, which include effects on movement, memory, pain and smooth muscle contractility. The

discovery of the cannabinoid signalling system in mammals has prompted investigation of the occurrence of this pathway in non-mammalian animals. Here we review the evidence for the existence of cannabinoid receptors in non-mammalian vertebrates and invertebrates and discuss the evolution of the cannabinoid signalling system. Genes encoding orthologues of the mammalian CB1 receptor have been identified in a fish, an amphibian and a bird, indicating that CB1 receptors may occur throughout the vertebrates. Pharmacological actions of cannabinoids and specific binding sites for cannabinoids have been reported in several invertebrate species, but the molecular basis for these effects is not known. Importantly, however, the genomes of the protostomian invertebrates *Drosophila melanogaster* and *Caenorhabditis elegans* do not contain CB1 orthologues, indicating that CB1-like cannabinoid receptors may have evolved after the divergence of deuterostomes (e.g. vertebrates and echinoderms) and protostomes. Phylogenetic analysis of the relationship of vertebrate CB1 receptors with other G-protein-coupled receptors reveals that the paralogues that appear to share the most recent common evolutionary origin with CB1 are lysophospholipid receptors, melanocortin receptors and adenosine receptors. Interestingly, as with CB1, each of these receptor types does not appear to have *Drosophila* orthologues, indicating that this group of receptors may not occur in protostomian invertebrates. We conclude that the cannabinoid signalling system may be quite restricted in its phylogenetic distribution, probably occurring only in the deuterostomian clade of the animal kingdom and possibly only in vertebrates.

British Journal Of Psychiatry • February 2001

Psychiatric effects of cannabis

By A. Johns

Department of Forensic Psychiatry, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

Full text with 58 references

<http://bjp.rcpsych.org/content/178/2/116.long>

Cannabis is commonly regarded as an innocuous drug and the prevalence of lifetime and regular use has increased in most developed countries. However, accumulative evidence highlights the risks of dependence and other adverse effects, particularly among people with pre-existing psychiatric disorders.

An appreciable proportion of cannabis users report short-lived adverse effects, including psychotic states following heavy consumption, and regular users are at risk of dependence. People with major mental illnesses such as schizophrenia are especially vulnerable in that cannabis generally provokes relapse and aggravates existing symptoms. Health workers need to recognise, and respond to, the adverse effects of cannabis on mental health.

Cannabis and health

By Michael Farrell and Bruce Ritson

Full text with references

<http://bjp.rcpsych.org/content/178/2/98>

Cannabis is the most commonly consumed illegal drug and self-reported consumption has continued to grow through the 1990s (Farrell et al, 1998). There is little controversy around the reported rise in its use but also little clarity about what has driven this rise. The health effects of cannabis can be discussed with greater dispassion as evidence accumulates. This evidence ranges from discussion on the long-term health effects of cannabis to the debate on the potential therapeutic benefits of cannabinoids in some medical conditions.

Discussions on the health effects of cannabis have often been the lynchpin of the other key debate on the legal status of cannabis. Indeed, it has been argued that the scientific investigation and deliberation on the health effects would resolve decisions on whether to legalise or not. The papers in this issue on the legal, social, psychological, pharmacological and therapeutic aspects of cannabis indicate the complexity of the debate which clearly has no simple right or wrong answer. There is mounting evidence of the adverse physical effects (Ashton, 2001, this issue) and the psychological effects of cannabis (Hall & Solowij, 1998; Johns, 2001, this issue). However, while there is need for an awareness of the negative effects, they are not impressive compared to the adverse effects of tobacco and alcohol misuse. This is not to argue that cannabis should be given the same status as tobacco and alcohol but to recognise a factual comparison. There is a tendency among the proponents of cannabis legalisation to argue that cannabis is devoid of adverse health effects and to ignore the evidence that cannabis itself can induce significant levels of dependence (Hall & Solowij, 1998).

The social and legal status of cannabis cannot be determined simply by the claims for or against on health grounds. Indeed, one of the key determinants of legal status is likely to be social and moral attitudes to a range of psychoactive substances and the anxiety that some patterns of social behaviour are strongly linked. MacCoun & Reuter (2001, this issue) argue that The Netherlands has all but legalised cannabis by regulating its

supply through coffee shops. Such an approach is pragmatic. However, it is an unbalanced equation in that it sanctions the consumption of the drug but not the supply and so retains the broader criminal element within this arrangement. The data from The Netherlands are mixed in that they appear to indicate that the coffee shop arrangement has resulted in a form of commercialisation and marketing of cannabis which promotes its further use. It is unclear what effect this social policy has had in Europe as a whole. However, it also indicates that the ready supply of cannabis has not fed the growth of an illegal drugs market to the extent that would concern individuals with serious reservations about changing the current control approach to cannabis.

Added to this is a fresh debate with contributors such as the House of Lords Technical Committee and the British Medical Association on the therapeutic use of cannabis and other cannabinoids. There is a clear need for an evidence-based approach to the therapeutic use of these compounds.

Robson's (2001, this issue) call for compassionate cannabis prescribing is attractive. But it risks placing a complex social problem within an inappropriate medical framework which, while surmounting immediate problems, is unlikely to be the long-term solution to the therapeutic use of cannabis. Studies have begun under the aegis of the Pharmaceutical Society which may go some way towards an evidence-based debate on the therapeutic use of cannabis. However, it is likely that in the longer term the issue of cannabis for a range of medical disorders will be seen as a medicinal matter, as is the case with homoeopathy and other complementary medicines. The therapeutic role of cannabinoids will require separate evaluation.

The body of knowledge on cannabis and cannabinoids continues to grow. The social response to it will be shaped by changing social values along with greater clarity of the issues involved.

The British Journal of Psychiatry • February 2001

Therapeutic aspects of cannabis and cannabinoids

By Philip Robson

Review commissioned in 1996 by the Department of Health (DOH)

Full text with 57 references

<http://bjp.rcpsych.org/content/178/2/107>

Cannabis and some cannabinoids are effective anti-emetics and analgesics and reduce intra-ocular pressure. There is evidence of symptom relief and improved well-being in selected neurological conditions, AIDS and certain cancers. Cannabinoids may reduce anxiety and improve sleep. Anticonvulsant activity requires clarification. Other properties identified by basic research await evaluation. Standard treatments for many relevant disorders are unsatisfactory. Cannabis is safe in overdose but often produces unwanted effects, typically sedation, intoxication, clumsiness, dizziness, dry mouth, lowered blood pressure or increased heart rate. The discovery of specific receptors and natural ligands may lead to drug developments. Research is needed to optimise dose and route of administration, quantify therapeutic and adverse effects, and examine interactions.

In 1996 I was commissioned by the Department of Health (DOH) to review the scientific literature regarding the potential therapeutic utility of cannabis and its derivatives. The review was based upon primary sources (identified from a Medline literature search, reference lists supplied by the DOH and the Institute for the Study of Drug Dependence, and personal communications with relevant academics and clinicians). This paper is a greatly shortened version of the review. The 4 years which have elapsed have seen little in the way of new clinical results but considerable advances in cannabinoid basic science (Institute of Medicine, 1999). Government licences have recently been granted for several controlled trials of both synthetic and plant-derived cannabinoids in multiple sclerosis and chronic pain. In January 2000, I was appointed Medical Director of GW Pharmaceuticals, a company established to derive medicinal extracts from standardised cannabis plants.

Neurotoxicology And Teratology • January 2001

**A literature review of the consequences of prenatal marihuana exposure.
An emerging theme of a deficiency in aspects of executive function**

Fried PA1, Smith AM.

Department of Psychology, Carleton University, K1S 5B6, Ottawa, Ontario, Canada
peter_fried@carleton.ca

<http://www.ncbi.nlm.nih.gov/pubmed/11274871>

In spite of marihuana being the most widely used illegal drug among women of reproductive age, there is a relative paucity of literature dealing with the neurobehavioral consequences in offspring--particularly the longer-term effects. However, there is a degree of consistency in the limited data, both across cross-sectional reports and longitudinally, where offspring have been followed for a number of years. Two cohort studies fall into the latter category; one involving a low-risk sample and, the other, a high-risk sample. Global IQ is not impacted by prenatal marihuana exposure but aspects of executive function (EF)--in particular, attentional behavior and visual analysis/hypothesis testing--appear to be negatively associated with in utero cannabis exposure in children beyond the toddler stage. This hypothesized influence of prenatal marihuana on EF is examined and discussed relative to effects (or lack of effects) across different ages in the offspring, cannabinoid receptors, and the extant general marihuana and prefrontal literature.

Addiction • November 2000

Initiation and progression of cannabis use in a population-based Australian adolescent longitudinal study

Coffey C1, Lynskey M, Wolfe R, Patton GC.

Centre for Adolescent Health, Department of Paediatrics, University of Melbourne, 2 Gatehouse Street, Parkville 3052, Australia

<http://www.ncbi.nlm.nih.gov/pubmed/11219371>

Peer cannabis use, daily smoking, alcohol use, antisocial behaviour and high rates of school-level cannabis use were associated with mid-school cannabis use and independently predicted late-school uptake. Cannabis use persisted into late-school use in 80% of all mid-school users. Persisting cannabis use from mid- to late-school was more likely in regular users (odds ratio (OR) 3.4), cigarette smokers (OR any smoking: 2.0, daily smoking: 3.3) and those reporting peer use (OR 2.1). Mid-school peer use independently predicted incident late-school daily use in males (OR 6.5) while high-dose alcohol use (OR 6.1) and antisocial behaviour (OR 6.6) predicted incident late-school daily use in females.

Most cannabis use remained occasional during adolescence but escalation to potentially harmful daily use in the late-school period occurred in 12% of early users. Transition was more likely in males, for whom availability and peer use were determinants. In contrast, females with multiple extreme behaviours were more likely to become daily users. Cigarette smoking was an important predictor of both initiation and persisting cannabis use.

Nature • March 2000

Cannabinoids control spasticity and tremor in a multiple sclerosis model

Baker D1, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, Layward L.

1. Department of Neurochemistry, Institute of Neurology, University College London, UK
D.Baker@ion.ucl.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/10716447>

Chronic relapsing experimental allergic encephalomyelitis (CREAE) is an autoimmune model of multiple sclerosis. Although both these diseases are typified by relapsing-remitting paralytic episodes, after CREAE induction by sensitization to myelin antigens Biozzi ABH mice also develop spasticity and tremor. These symptoms also occur during multiple sclerosis and are difficult to control. This has prompted some patients to find alternative medicines, and to perceive benefit from cannabis use. Although this benefit has been backed up by small clinical studies, mainly with non-quantifiable outcomes, the value of cannabis use in multiple sclerosis remains anecdotal. Here we show that cannabinoid (CB) receptor agonism using R(+)-WIN 55,212, delta9-tetrahydrocannabinol, methanandamide and JWH-133 (ref. 8) quantitatively ameliorated both tremor and spasticity in diseased mice. The exacerbation of these signs after antagonism of the CB1 and CB2 receptors, notably the CB1 receptor, using SR141716A and SR144528 (ref. 8) indicate that the endogenous cannabinoid system may be tonically active in the control of tremor and spasticity. This provides a rationale for patients' indications of the therapeutic potential of cannabis in the control of the symptoms of multiple sclerosis, and provides a means of evaluating more selective cannabinoids in the future.

Drug Alcohol Dependency • February 2000

An approach to the medical marijuana controversy

By L.E. Hollister

University of Texas Medical Branch, UT Harris County Psychiatric Center, Houston 77021, USA

<http://www.ncbi.nlm.nih.gov/pubmed/10669050>

The use of smoked marijuana as a therapeutic agent is presently a matter of considerable debate in the United States. Many people suffering from a variety of disorders maintain that it is necessary for their adequate treatment. Yet, the evidence to support claims is insufficient for FDA approval. An interim solution is proposed which would allow patients referred by their physicians to participate in a 6-month program of legal marijuana availability, similar to the 'compassionate IND' program of a number of years ago. A technique similar to that used for post-marketing surveillance is proposed for obtaining quantitative data for a limited number of potential indications. These are: (1) nausea and vomiting associated with cancer chemotherapy or other causes, (2) weight loss associated with debilitating illnesses, (3) spasticity secondary to neurological diseases, and (4) chronic pain syndromes.

Neuroreport • February 2000

Effects of frequent marijuana use on brain tissue volume and composition

Block RI1, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, Hall JA.

Department of Anesthesia, University of Iowa, Iowa City 52242-1100, USA

<http://www.ncbi.nlm.nih.gov/pubmed/10718301>

To investigate CNS effects of frequent marijuana use, brain tissue volume and composition were measured using magnetic resonance imaging (MRI) in 18 current, frequent, young adult marijuana users and 13 comparable, non-using controls. Automated image analysis techniques were used to measure global and regional brain volumes, including, for most regions, separate measures of gray and white matter. The marijuana users showed no evidence of cerebral atrophy or global or regional changes in tissue volumes. Volumes of ventricular CSF were not higher in marijuana users than controls, but were, in fact, lower. There were no clinically significant abnormalities in any subject's MRI. Sex differences were detected in several global volume measures.

Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997

ElSohly MA¹, Ross SA, Mehmedic Z, Arafat R, Yi B, Banahan BF 3rd.

National Center for The Development of Natural Products, Research Institute of Pharmaceutical Sciences, Departments of Pharmaceutics, University of Mississippi, USA

<http://www.ncbi.nlm.nih.gov/pubmed/10641915>

The analysis of 35,312 cannabis preparations confiscated in the USA over a period of 18 years for delta-9-tetrahydrocannabinol (delta9-THC) and other major cannabinoids is reported. Samples were identified as cannabis, hashish, or hash oil. Cannabis samples were further subdivided into marijuana (loose material, kilobricks and buds), sinsemilla, Thai sticks and ditchweed. The data showed that more than 82% of all confiscated samples were in the marijuana category for every year except 1980 (61%) and 1981 (75%). The potency (concentration of delta9-THC) of marijuana samples rose from less than 1.5% in 1980 to approximately 3.3% in 1983 and 1984, then fluctuated around 3% till 1992. Since 1992, the potency of confiscated marijuana samples has continuously risen, going from 3.1% in 1992 to 4.2% in 1997. The average concentration of delta9-THC in all cannabis samples showed a gradual rise from 3% in 1991 to 4.47% in 1997. Hashish and hash oil, on the other hand, showed no specific potency trends. Other major cannabinoids [cannabidiol (CBD), cannabinol (CBN), and cannabichromene (CBC)] showed no significant change in their concentration over the years.

Journal Of Public Health Policy • January 2000

The ethics of medical marijuana: government restrictions vs. medical necessity

By P.A. Clark

Saint Joseph's Philadelphia's Jesuit University, Pennsylvania 19131-1395, USA

<http://www.ncbi.nlm.nih.gov/pubmed/10754797>

Marijuana is listed by the Drug Enforcement Agency (DEA) as an illegal Schedule I drug which has no currently accepted medical use. However, on March 17, 1999, 11 independent scientists appointed by the Institute of Medicine reported that medical marijuana was effective in controlling some forms of pain, alleviating nausea and vomiting due to chemotherapy, treating wasting due to AIDS, and combating muscle spasms associated with multiple sclerosis. There was also no evidence that using marijuana would increase illicit drug use or that it was a "gateway" drug. Despite this evidence the DEA refuses to reclassify marijuana as a Schedule II drug, which would allow physicians to prescribe unadulterated and standardized forms of marijuana. After reviewing the pertinent scientific data and applying the principle of double effect, there is a proportionate reason for allowing physicians to prescribe marijuana. Seriously ill patients have the right to effective therapies. To deny patients access to such a therapy is to deny them dignity and respect as persons.

Addiction Biology • January 2000

Neuropharmacology and therapeutic potential of cannabinoids

By R.G. Pertwee

Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK
rgp@aberdeen.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/20575818>

Mammalian tissues contain at least two types of cannabinoid receptor, CB₁, found mainly on neurones and CB₂, found mainly in immune cells. Endogenous ligands for these receptors have also been identified. These endocannabinoids and their receptors constitute the endogenous cannabinoid system. Two cannabinoid receptor agonists, Δ^9 -tetrahydrocannabinol and nabilone, are used clinically as anti-emetics or to boost appetite. Additional therapeutic uses of cannabinoids may include the suppression of some multiple sclerosis and spinal injury symptoms, the management of pain, bronchial asthma and glaucoma, and the prevention of neurotoxicity. There are also potential clinical applications for CB₁ receptor antagonists, in the management of acute schizophrenia and cognitive/memory dysfunctions and as appetite suppressants. Future research is likely to be directed at characterizing the endogenous cannabinoid system more completely, at obtaining more conclusive clinical data about cannabinoids with regard to both beneficial and adverse effects, at developing improved cannabinoid formulations and modes of administration for use in the clinic and at devising clinical strategies for separating out the sought-after effects of CB₁ receptor agonists from their psychotropic and other unwanted effects.

Marijuana use and increased risk of squamous cell carcinoma of the head and neck

Zhang ZF1, Morgenstern H, Spitz MR, Tashkin DP, Yu GP, Marshall JR, Hsu TC, Schantz SP.

Department of Epidemiology, University of California at Los Angeles School of Public Health, and Jonsson Comprehensive Cancer Center, 90095-1772, USA
zfzhang@ucla.edu

Full text, PDF, with 41 references

<http://cebp.aacrjournals.org/content/8/12/1071.full.pdf>

Marijuana is the most commonly used illegal drug in the United States. In some subcultures, it is widely perceived to be harmless. Although the carcinogenic properties of marijuana smoke are similar to those of tobacco, no epidemiological studies of the relationship between marijuana use and head and neck cancer have been published.

The relationship between marijuana use and head and neck cancer was investigated by a case-control study of 173 previously untreated cases with pathologically confirmed diagnoses of squamous cell carcinoma of the head and neck and 176 cancer-free controls at Memorial Sloan-Kettering Cancer Center between 1992 and 1994. Epidemiological data were collected by using a structured questionnaire, which included history of tobacco smoking, alcohol use, and marijuana use. The associations between marijuana use and head and neck cancer were analyzed by Mantel-Haenszel methods and logistic regression models. Controlling for age, sex, race, education, alcohol consumption, pack-years of

cigarette smoking, and passive smoking, the risk of squamous cell carcinoma of the head and neck was increased with marijuana use [odds ratio (OR) comparing ever with never users, 2.6; 95% confidence interval (CI), 1.1-6.6]. Dose-response relationships were observed for frequency of marijuana use/day (P for trend <0.05) and years of marijuana use (P for trend <0.05). These associations were stronger for subjects who were 55 years of age and younger (OR, 3.1; 95% CI, 1.0-9.7). Possible interaction effects of marijuana use were observed with cigarette smoking, mutagen sensitivity, and to a lesser extent, alcohol use.

Our results suggest that marijuana use may increase the risk of head and neck cancer with a strong dose-response pattern. Our analysis indicated that marijuana use may interact with mutagen sensitivity and other risk factors to increase the risk of head and neck cancer. The results need to be interpreted with some caution in drawing causal inferences because of certain methodological limitations, especially with regard to interactions.

Behavioral effects of cannabinoid agents in animals

Chaperon F1, Thiébot MH.

INSERM U.288 and Department of Pharmacology, Faculty of Medicine Pitié-Salpêtrière, Paris, France

<http://www.ncbi.nlm.nih.gov/pubmed/10803637>

Two subtypes of cannabinoid receptors have been identified to date, the CB1 receptor, essentially located in the CNS, but also in peripheral tissues, and the CB2 receptor, found only at the periphery. The identification of delta9-tetrahydrocannabinol (delta9-THC) as the major active component of marijuana (*Cannabis sativa*), the recent emergence of potent synthetic ligands and the identification of anandamide and sn-2 arachidonylglycerol as putative endogenous ligands for cannabinoid receptors in the brain, have contributed to advancing cannabinoid pharmacology and approaching the neurobiological mechanisms involved in physiological and behavioral effects of cannabinoids. Most of the agonists exhibit nonselective affinity for CB1/CB2 receptors, and delta9-THC and anandamide probably act as partial agonists. Some recently synthesized molecules are highly selective for CB2 receptors, whereas selective agonists for the CB1 receptors are not yet available. A small number of antagonists exist that display a high selectivity for either CB1 or CB2 receptors. Cannabinomimetics produce complex pharmacological and behavioral effects that probably involve numerous neuronal substrates. Interactions with dopamine, acetylcholine, opiate, and GABAergic systems have been demonstrated in several brain structures. In animals, cannabinoid agonists such as delta9-THC, WIN 55,212-2, and CP 55,940 produce a characteristic combination of four symptoms, hypothermia, analgesia, hypoactivity, and catalepsy. They are reversed by the selective CB1 receptor antagonist, SR 141716, providing good evidence for the involvement of CB1-related mechanisms. Anandamide exhibits several differences, compared with other agonists. In particular, hypothermia, analgesia, and catalepsy induced by this endogenous ligand are not reversed by SR 141716. Cannabinoid-related processes seem also involved in cognition, memory, anxiety, control of appetite, emesis, inflammatory, and immune responses. Agonists may induce biphasic effects, for example, hyperactivity at low doses and severe motor deficits at larger doses. Intriguingly, although cannabis is widely used as recreational drug in humans, only a few studies revealed an appetitive potential of cannabimimetics in animals, and evidence for aversive effects of delta9-THC, WIN 55,212-2, and CP 55,940 is more readily obtained in a variety of tests. The selective blockade of CB1 receptors by SR 141716 impaired the perception of the appetitive value of positive reinforcers (food, cocaine, morphine) and reduced the motivation for sucrose, beer and alcohol consumption, indicating that positive incentive and/or motivational processes could be under a permissive control of CB1-related mechanisms. There is little evidence that cannabinoid systems are activated under basal conditions. However, by using SR 141716 as a tool, a tonic involvement of a CB1-mediated cannabinoid link has been demonstrated, notably in animals suffering from chronic pain, faced with anxiogenic stimuli or highly motivational reinforcers. Some effects of SR 141716 also suggest that CB1-related mechanisms exert a tonic control on cognitive processes. Extensive basic research is still needed to elucidate the roles of cannabinoid systems, both in the brain and at the periphery, in normal physiology and in diseases. Additional compounds, such as selective CB1 receptor agonists, ligands that do not cross the blood brain barrier, drugs interfering with synthesis, degradation or uptake of endogenous ligand(s) of CB receptors, are especially needed to understand when and how cannabinoid systems are activated. In turn, new therapeutic strategies would likely to emerge.

Cannabis and cannabinoids: pharmacology and rationale for clinical use

By R. G. Pertwee

Institute of Biomedical Sciences, Aberdeen, Scotland
rgp@aberdeen.ac.uk

<http://www.ncbi.nlm.nih.gov/pubmed/10575283>

It is now known that there are at least two types of cannabinoid receptors. These are CB1 receptors, present mainly on central and peripheral neurones, and CB2 receptors, present mainly on immune cells. Endogenous cannabinoid receptor agonists ('endocannabinoids') have also been identified. The discovery of this 'endogenous cannabinoid system' has led to the development of selective CB1 and CB2 receptor ligands and fueled renewed interest in the clinical potential of cannabinoids. Two cannabinoid CB1 receptor agonists are already used clinically, as antiemetics or as appetite stimulants. These are D 9 - tetrahydrocannabinol (THC) and nabilone. Other possible uses for CB1 receptor agonists include the suppression of muscle spasm/spasticity associated with multiple sclerosis or spinal cord injury, the relief of chronic pain and the management of glaucoma and bronchial asthma. CB1 receptor antagonists may also have clinical applications, e. g. as appetite suppressants and in the management of schizophrenia or disorders of cognition and memory. So too may CB2 receptor ligands and drugs that activate cannabinoid receptors indirectly by augmenting endocannabinoid levels at cannabinoid receptors. When taken orally, THC seems to undergo variable absorption and to have a narrow 'therapeutic window' (dose range in which it is effective without producing significant unwanted effects). This makes it difficult to predict an oral dose that will be both effective and tolerable to a patient and indicates a need for better cannabinoid formulations and modes of administration. For the therapeutic potential of cannabis or CB1 receptor agonists to be fully exploited, it will be important to establish objectively and conclusively (a) whether these agents have efficacy against selected symptoms that is of clinical significance and, if so, whether the benefits outweigh the risks, (b) whether cannabis has therapeutic advantages over individual cannabinoids, (c) whether there is a need for additional drug treatments to manage any of the disorders against which cannabinoids are effective, and (d) whether it will be possible to develop drugs that have reduced psychotropic activity and yet retain the ability to act through CB1 receptors to produce their sought-after effects.

Cannabis: discrimination of “internal bliss”?

By J.L. Wiley

Virginia Commonwealth University, Department of Pharmacology & Toxicology, Richmond 23298-0613, USA

<http://www.ncbi.nlm.nih.gov/pubmed/10515300>

The recent discovery of arachidonylethanolamide (anandamide), an endogenous ligand for cannabinoid receptors, and the synthesis of SR141716A, a cannabinoid antagonist selective for brain cannabinoid (CB1) receptors, have provided new tools to explore the mechanisms underlying cannabis abuse and dependence. Drug discrimination is the animal model with the most predictive validity and specificity for investigation of the psychoactive effects of cannabinoids related to their abuse potential, because, unlike many other drugs of abuse, delta9-tetrahydrocannabinol (delta9-THC), the major psychoactive ingredient of marijuana, is not self-administered by animals. Results of delta9-THC discrimination studies have revealed that the subjective effects of cannabis intoxication are pharmacologically selective for centrally active cannabinoid compounds, and that cannabis action at CB1 receptors is involved in medication of these effects. Less clear is the role of endogenous cannabinoid system(s) in cannabis intoxication. Anandamide, named for a Sanskrit word for “internal bliss,” unreliably substitutes for delta9-THC. Further, substitution, when it is observed, occurs only at doses that also significantly decrease response rates. In contrast, delta9-THC and other structurally diverse cannabinoids fully substitute for delta9-THC at doses that do not substantially affect response rates. Attempts to train animals to discriminate anandamide (or SR141716A) have so far been unsuccessful. Preliminary evidence from drug discrimination studies with more metabolically stable anandamide analogs have suggested that these differences in the discriminative stimulus effects of delta9-THC and anandamide-like cannabinoids are not entirely due to pharmacokinetic factors, but the exact role of “internal bliss” in cannabis intoxication and dependence is still not completely understood.

Mechanism of cannabinoid effects on long-term potentiation and depression in hippocampal CA1 neurons

Misner DL1, Sullivan JM.

Molecular Neurobiology Laboratory, The Salk Institute, La Jolla, California 92037, USA

Full text with 48 references

<http://www.jneurosci.org/content/19/16/6795.long>

Cannabinoids, the active constituents of marijuana, are known to impair learning and memory. Receptors for cannabinoids are highly expressed in the hippocampus, a brain region that is believed to play an important role in certain forms of learning and memory. To investigate the possible contribution of cannabinoid receptor-mediated deficits in hippocampal function to the learning and memory impairments produced by marijuana, we studied the effects of cannabinoid receptor activation on two models of learning and memory, long-term potentiation (LTP) and long-term depression (LTD), in hippocampal slices. Although LTP and LTD of CA1 field potentials were blocked by cannabinoid receptor activation in the presence of Mg(2+), they could be induced after Mg(2+) was removed. Similarly, LTP and LTD of whole-cell EPSCs were unimpaired in the presence of cannabinoid receptor agonist when the postsynaptic membrane was depolarized during the LTP or LTD induction protocol. Cannabinoid receptor activation also reduced EPSCs and enhanced paired-pulse facilitation, while having no effect on the amplitude of spontaneous miniature EPSCs. Finally, as with cannabinoid receptor activation, inhibition of LTP by adenosine receptor activation could be overcome by removal of Mg(2+) or depolarization of the postsynaptic membrane during tetanus. Our results indicate that cannabinoid receptor activation does not directly inhibit the molecular mechanisms responsible for long-term synaptic plasticity but instead impairs LTP and LTD by reducing presynaptic neurotransmitter release to a level below that required to depolarize the postsynaptic membrane to relieve Mg(2+) blockade of NMDA receptors.

Δ^9 -Tetrahydrocannabinol induces apoptosis in C6 glioma cells

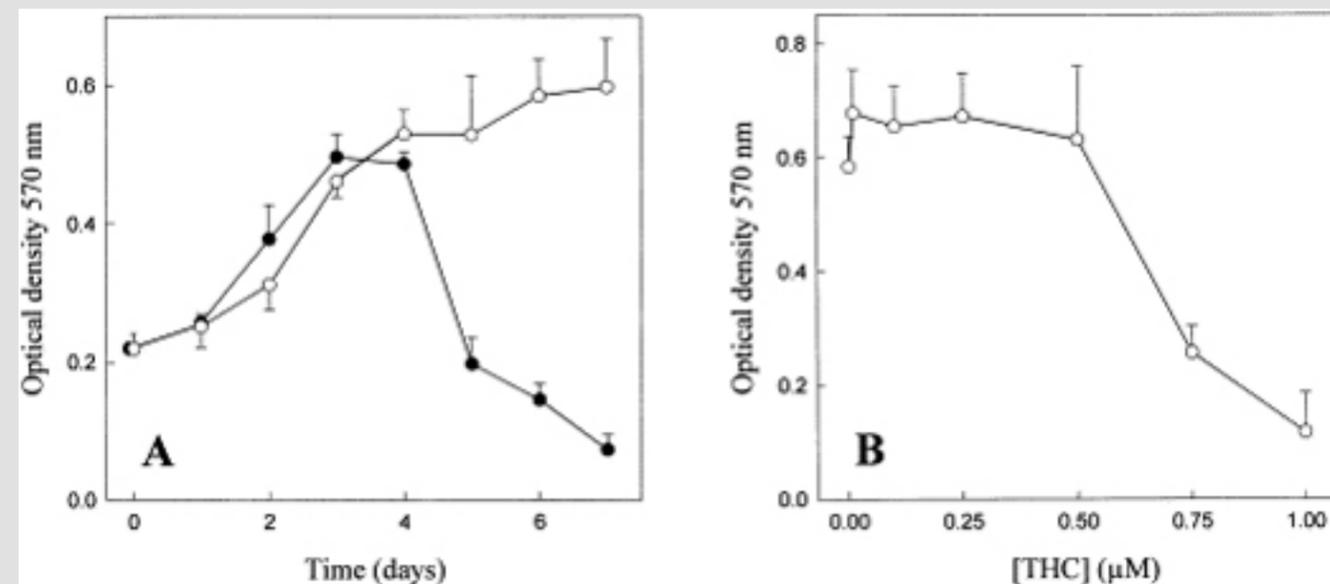
Sánchez C1, Galve-Roperh I, Canova C, Brachet P, Guzmán M.

Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain

Full text with 29 references

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delta9-Tetrahydrocannabinol (THC), the major active component of marijuana, induced apoptosis in C6.9 glioma cells, as determined by DNA fragmentation and loss of plasma membrane asymmetry. THC stimulated sphingomyelin hydrolysis in C6.9 glioma cells. THC and N-acetylsphingosine, a cell-permeable ceramide analog, induced apoptosis in several transformed neural cells but not in primary astrocytes or neurons. Although glioma C6.9 cells expressed the CBI cannabinoid receptor, neither THC-induced apoptosis nor THC-induced sphingomyelin breakdown were prevented by SR141716, a specific antagonist of that receptor. Results thus show that THC-induced apoptosis in glioma C6.9 cells may rely on a CBI receptor-independent stimulation of sphingomyelin breakdown.



THC-induced depression of mitochondrial oxidative metabolism in C6.9 glioma cells. A: Cells were cultured in serum-free medium in the absence (○) or in the presence (●) of 1 μM THC for the times indicated. B: Cells were cultured in serum-free medium in the presence of the indicated concentrations of THC for 5 days. In all cases, the medium was renewed every 48 h. The mitochondrial redox state was assessed by the MTT test as the optical density at 570 nm. Results correspond to 4 different experiments.

Western Journal Of Medicine • June 1998

Medical Marijuana

By J.B. Marmor

Department of Radiation Oncology, Sequoia Hospital, Redwood City California 94062-2799, USA
jbm@marmor.org

Full text with 16 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1305083/>

Although many clinical studies suggest the medical utility of marijuana for some conditions, the scientific evidence is weak. Many patients in California are self-medicating with marijuana, and physicians need data to assess the risks and benefits. The only reasonable solution to this problem is to encourage research on the medical effects of marijuana. The current regulatory system should be modified to remove barriers to clinical research with marijuana. The NIH panel has identified several conditions for which there may be therapeutic benefit from marijuana use and that merit further research. Marijuana should be held to the same evaluation standards of safety and efficacy as other drugs (a major flaw in Proposition 215) but should not have to be proved better than current medications for its use to be adopted. The therapeutic window for marijuana and THC between desired effect and unpleasant side effects is narrow and is a major reason for discontinuing use. Although the inhaled route of administration has the benefit of allowing patients to self-titrate the dose, the smoking of crude plant material is problematic. The NIH panel recommended that a high priority be given to the development of a controlled inhaled form of THC. The presence of a naturally occurring cannabinoid-receptor system in the brain suggests that research on selective analogues of THC may be useful to enhance its therapeutic effects and minimize adverse effects.

Neurotoxicology And Teratology • May 1998

Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana

Fried PA1, Watkinson B, Gray R.

Department of Psychology, Carleton University, Ottawa, Ontario, Canada
pfried@ccs.carleton.ca

<http://www.ncbi.nlm.nih.gov/pubmed/9638687>

Cognitive performance was examined in 131 9-12-year-old children for whom prenatal marihuana and cigarette exposure had been ascertained. The subjects, participants in an ongoing longitudinal study, were from a low-risk, predominantly middle class sample. The tasks included the WISC-III and a series of tests assessing aspects of cognition subsumed under the rubric of executive function. Consistent with results obtained at earlier ages, discriminant function analysis revealed a dose-dependent association, which remained after controlling for potential confounds (including secondhand smoke), between prenatal cigarette exposure and lower global intelligence scores with the verbal subtests of the WISC maximally discriminating among levels of in utero exposure. In contrast, prenatal marihuana exposure was not associated with global intelligence or the verbal subtests. Rather, this drug was negatively associated with the executive function tasks that require impulse control and visual analysis/hypothesis testing and with a number of WISC subtests requiring the same abilities. The interpretation of these results is discussed in terms of executive function and is related to earlier observations of this sample and to the extant prefrontal and general marihuana literature.

SR 144528, the first potent and selective antagonist of the CB2 cannabinoid receptor

Rinaldi-Carmona M1, Barth F, Millan J, Derocq JM, Casellas P, Congy C, Oustric D, Sarran M, Bouaboula M, Calandra B, Portier M, Shire D, Brelière JC, Le Fur GL.

1. Sanofi Recherche, 34184 Montpellier Cedex 04 (France) and Sanofi Recherche, Labège-Innopole voie1, BP137, 31676 Labège, Cédex 04 (France)

Full text with 34 references

<http://jpet.aspetjournals.org/content/284/2/644.long>

Based on both binding and functional data, this study introduces SR 144528 as the first, highly potent, selective and orally active antagonist for the CB2 receptor. This compound which displays subnanomolar affinity ($K_i = 0.6$ nM) for both the rat spleen and cloned human CB2 receptors has a 700-fold lower affinity ($K_i = 400$ nM) for both the rat brain and cloned human CB1 receptors. Furthermore it shows no affinity for any of the more than 70 receptors, ion channels or enzymes investigated ($IC_{50} > 10$ microM). In vitro, SR 144528 antagonizes the inhibitory effects of the cannabinoid receptor agonist CP 55,940 on forskolin-stimulated adenylyl cyclase activity in cell lines permanently expressing the h CB2 receptor ($EC_{50} = 10$ nM) but not in cells expressing the h CB1 (no effect at 10 microM). Furthermore, SR 144528 is able to selectively block the mitogen-activated protein kinase activity induced by CP 55,940 in cell lines expressing h CB2 ($IC_{50} = 39$ nM) whereas in cells expressing h CB1 an IC_{50} value of more than 1 microM is found. In addition, SR 144528 is shown to antagonize the stimulating effects of CP 55,940 on human tonsillar B-cell activation evoked by cross-linking of surface Igs ($IC_{50} = 20$ nM). In vivo, after oral administration SR 144528 totally displaced the ex vivo [3H]-CP 55,940 binding to mouse spleen membranes ($ED_{50} = 0.35$ mg/kg) with a long duration of action. In contrast, after the oral route it does not interact with the cannabinoid receptor expressed in the mouse brain (CB1). It is expected that SR 144528 will provide a powerful tool to investigate the in vivo functions of the cannabinoid system in the immune response.

Journal Of Paediatric Child Health • February 1998

Cannabis and brain function

By J.M. Court

Centre for Adolescent Health, Royal Children's Hospital, Parkville, Victoria, Australia

<http://www.ncbi.nlm.nih.gov/pubmed/9568931>

Current literature and practice experience has been reviewed to clarify what is known about the effects of cannabis on brain function, the risk that cannabis use may pose for young people during their adolescence, and risk factors within the individual or their environment that may predispose to long-term abuse and dependence. There is sound evidence that cannabis intoxication has an adverse effect on cognitive function and behaviour, and may, in vulnerable individuals, lead to a psychotic reaction. Regular use may have an adverse effect on learning, with possible mid- to long-term psychological and cognitive impairment. Heavy use may lead to emotional dependence with consequent social and psychological dysfunction. Intervention strategies must go beyond the conventional education and public health measures that appear to have been unsuccessful so far in influencing cannabis use in teenagers. Such strategies may more usefully aim at assessment of risk factors in individuals and groups for dependence on the drug, and the combined and cooperative intervention of parents, schools, health professionals and teenagers themselves.

Critical Reviews In Neurobiology • January 1997

Molecular aspects of cannabinoid receptors

By L.A. Matsuda

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston 29425, USA

<http://www.ncbi.nlm.nih.gov/pubmed/9209828>

Two cannabinoid receptors are reviewed with regard to their primary structure, ligand-binding properties, and signal transduction systems. Both receptors have been cloned; therefore, the expression of their genes and the functional domains within the proteins can be examined. Binding of tritiated agonists has localized these receptors to the central nervous and immune systems. The CB1 receptor is predominantly expressed in brain tissues and is found in both glial elements and neurons; subcellular localization to axons and terminals is evident. This receptor is found in motor, limbic, associative, cognitive, sensory, and autonomic brain structures. CB1 receptors modulate the activities of calcium and potassium channels. The CB2 receptor is predominantly expressed in the immune system and is found in spleen, tonsils, thymus, mast cells, and blood cells. Although receptors appear to be involved in cannabimimetic-induced modulation of immune cell function, the receptor subtype that is principally involved in specific effects is difficult to determine because both receptors are often coexpressed in the same cells. Cannabimimetic-induced effects on mast cells and B cells appear, however, to be mediated by CB2 receptors.

Psychoactive cannabinoids increase mortality and alter acute phase cytokine responses in mice sublethally infected with *Legionella pneumophila*

Smith MS1, Yamamoto Y, Newton C, Friedman H, Klein T.

1. Department of Medical Microbiology and Immunology, University of South Florida College of Medicine, Tampa 33612, USA

<http://www.ncbi.nlm.nih.gov/pubmed/9012363>

Marijuana contains both psychoactive and nonpsychoactive cannabinoids which have varying effects on the immune response system. Previous studies with delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, showed that this substance augmented the susceptibility of mice to infection with the opportunistic pathogen *Legionella pneumophila*. The present study compared the enhancement of *Legionella*-induced mortality in mice due to two other major of marijuana components, cannabidiol and cannabidiol, as well as the synthetic psychoactive cannabinoid CP 55,940. Inbred BALB/c mice, relatively resistant to infection with *Legionella*, were given the marijuana component 1 day before and 1 day after a sublethal intravenous infection with *Legionella*. Unlike the effect of THC, an 8 mg/kg dose of either cannabidiol or cannabidiol did not affect mortality of the mice sublethally infected with *Legionella*. Mice given a 16 mg/kg dose of these components of marijuana, however, showed a slight to moderately increased mortality following the sublethal infection with *Legionella*. In contrast, a dose of 6 mg/kg of the synthetic psychoactive cannabinoid CP 55,940 given 1 day before and 1 day after infection with *Legionella* resulted in about 50% of the animals dying, the same level of augmentation of lethality induced by THC. Liver, spleen, and lung tissues were removed from the surviving mice 24 hr after the second THC injection and tested for the presence of viable *Legionella* using a standard CFU assay. The mice injected with THC before and after infection showed significantly higher levels of bacteria in their lung than mice that were not given any cannabinoid but were infected sublethally with the *Legionella*. Mice injected with the other cannabinoids, including the synthetic cannabinoid, showed a much smaller increase in the number of *Legionella* in their lung when infected with *Legionella* and treated with the drug. The number of bacteria recovered from the kidney and liver of the mice regardless of treatment with a cannabinoid, including with THC, did not show significant changes. RNA isolated from the spleen of the THC- and *Legionella*-treated animals was examined to determine at the molecular level whether acute phase pro-inflammatory cytokines (i.e., IL-1, IL-6 and TNF-alpha) were altered following drug treatment and infection, since previous studies had shown there were increased serum levels of these cytokines in the mice. It was found that the mRNA levels for IL-1 remained generally constant regardless of whether the infected animals were treated with a cannabinoid. However, the mRNA level for IL-6 was markedly increased following treatment of the infected animals with THC, suggesting the possible involvement of this pro-inflammatory cytokine in increased mortality. The mRNA level for TNF-alpha was generally low and not significantly altered in the drug treated animals. Mice given other cannabinoids, including cannabidiol and cannabidiol, as well as the synthetic CP 55,940, showed no significant change in the level of mRNA for any of the cytokines tested.

delta 9-Tetrahydrocannabinol, cytokines, and immunity to Legionella pneumophila

Klein TW¹, Newton C, Zhu W, Daaka Y, Friedman H.

1. Department of Medical Microbiology and Immunology, University of South Florida College of Medicine, Tampa 33612, USA

<http://www.ncbi.nlm.nih.gov/pubmed/7777582>

The major psychoactive component of marijuana, delta 9-tetrahydrocannabinol (THC), has been shown to suppress the functions of various immune cells. However, the relationship of these findings to THC-induced suppression of host resistance to infection has not been firmly established. In this report, we review the literature concerning THC's effects on cytokine production and resistance to infection with *Legionella pneumophila* (Lp). Recent reports have linked THC-induced immunomodulation with drug-induced modulation of the cytokine network. Specifically, THC in vivo suppresses interferon (IFN) production while in vitro modulates the production of tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-2 (IL-2), and interleukin-2 receptor (IL-2R). These results suggested that THC treatment might alter host immunity by disrupting the cytokine network. Immunity and resistance to infection with Lp depends upon the activation of killer cells and the stimulation of the cytokine network. THC injection into rodents was observed to augment acute phase cytokine mobilization in response to a primary Lp infection; on the other hand, the drug suppressed the development of protective immunity and resistance to secondary Lp infection by causing a change in the profile of T helper cell cytokines produced by Th1 and Th2 cells. Thus, it appears that THC injection suppresses resistance to Lp infection by disrupting the cytokine network. Regarding the molecular mechanisms of these effects of THC, data is reviewed concerning the role of cannabinoid receptors (CR) in cells of the immune system. In summary, the literature to date supports the role of THC as an immunomodulator capable of suppressing resistance to infection through mechanisms involving alteration of the cytokine network. The role of CR receptors in these events has yet to be determined.

Australian Journal Of Public Health • June 1995

The public health significance of cannabis use in Australia

By W. Hall

National Drug and Alcohol Research Centre, University of New South Wales, Sydney

<http://www.ncbi.nlm.nih.gov/pubmed/7626673>

A fair appraisal of the public health significance of cannabis use has been hampered by the polarised opinions about its health effects expressed by partisans on both sides of the debate on its legal status. The findings of a recent review of the literature on the adverse health and psychological effects of cannabis are used to estimate the major probable public health risks of cannabis use in Australia. These appear to be, in order of approximate public health importance: adverse psychological effects; motor vehicle accidents; cannabis dependence; respiratory disease; precipitation and exacerbation of schizophrenia in vulnerable individuals; low-birthweight babies; and perhaps subtle cognitive impairment. On current patterns of use, cannabis use is a modest public health concern by comparison with alcohol and tobacco, although given the scale of public health damage caused by the latter drugs, and the currently low prevalence of regular cannabis use, this is not cause for complacency.

Advances In Experimental Medicine And Biology • February 1995

Marijuana, receptors and immunomodulation

Friedman H1, Klein TW, Newton C, Daaka Y.

1. University of South Florida College of Medicine, Tampa, USA

<http://www.ncbi.nlm.nih.gov/pubmed/7668140>

THC, the major psychoactive component of marijuana, has been shown both in humans and experimental animals to have immunomodulatory properties. For example, marijuana smokers may show impaired immunological functions, including deficiency of blood leukocyte blastogenesis to mitogens. Detailed studies with mice have shown that animals given THC can show marked immunomodulation, including suppression of antibody formation, deficient cytokine production, etc. However, recent studies have also shown that lymphoid cells evince enhanced production or release of IL1, but suppression of IL2 and interferon production. Such lymphoid cells treated in vitro with THC also show suppressed blastogenesis to antigens and mitogens, suppressed NK activity, etc. In contrast, it has recently been shown that THC can enhance production or release of pro-inflammatory cytokines. This includes release of these cytokines from macrophages, including augmented release of IL1, TNF alpha, and IL6 activity. Susceptibility of mice to infection with opportunistic organisms such as *L. pneumophila* has been found and this increased susceptibility can be modulated by THC. A toxic shock-like death to *Legionella* has been induced by THC treatment given one day before and one day after infection. Receptors to THC have been detected in the brain as well as in peripheral tissues, including lymphoid cells. Thus, immunomodulation induced by THC may be related to receptor effects as well as unrelated to such receptors. It is clear that THC and other cannabinoids are excellent tools for studying the mechanisms of immune modulation, especially altered susceptibility to microbial infection.

Prenatal exposure to marihuana and tobacco during infancy, early and middle childhood: effects and an attempt at synthesis

By P.A. Fried

Department of Psychology, Carleton University, Ottawa, Ontario, Canada

<http://www.ncbi.nlm.nih.gov/pubmed/7786162>

Both marihuana and cigarettes appear implicated, in a differential fashion, in the neurobehaviour of infants and children born to women who used these substances during pregnancy. In a low-risk upper middle class sample, marihuana use was associated, in the newborn, with mild withdrawal symptoms and some autonomic disruption of nervous system state regulation. However, between 6 months and 3 years of age no behavioural consequences of marihuana exposure (once confounding factors were controlled) were noted. At four years of age, although global tests of intelligence did not differentiate exposed from non-marihuana exposed children, verbal ability and memory were associated with in utero marihuana exposure. At five and six years of age these general areas were also noted to be associated with maternal cannabis use as was sustained attention. These areas of neurobehavior that appear affected by marihuana exposure during fetal development are ones that are consistent with the cognitive construct of 'executive functioning' which is thought to be a marker of prefrontal lobe functioning. Consistent with the observations derived from these children is that prefrontal functioning may not be apparent until approximately four years of age and that executive functioning is disassociated from measures of global intelligence. Exposure to cigarettes during pregnancy appears to be associated with neurobehavioural deficits in the auditory domain. In the newborn this is manifested by decreased responsivity to sound and altered auditory habituation. Between the ages of one and 11 years the performance on auditory related tasks (verbal memory, language, auditory processing) were consistently the domains that differentiated the cigarette exposed from the non exposed children. The possible role of the cholinergic mediated efferent auditory system is discussed. Also associated with in utero exposure to cigarettes were general cognitive performance and parental reports and objectively derived measures of impulsivity. The striking degree of consistency over the years lends strength to the interpretation that the observations in childhood have, at least as their partial etiology, the prenatal exposure to cigarettes. However, in interpreting the evidence presented it must be recognized that the alterations in the child's behaviour may well affect the parenting behaviour. This potential transactional interaction must remain an integral part of drawing conclusions about both marihuana and cigarette's effects.

FEBS Letters • August 1994

SR141716A, a potent and selective antagonist of the brain cannabinoid receptor

Rinaldi-Carmona M1, Barth F, Héaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Néliat G, Caput D, et al.

1. Sanofi Recherche, Montpellier, France

Full text with 26 references

[http://onlinelibrary.wiley.com/doi/10.1016/0014-5793\(94\)00773-X/epdf](http://onlinelibrary.wiley.com/doi/10.1016/0014-5793(94)00773-X/epdf)

SR141716A is the first selective and orally active antagonist of the brain cannabinoid receptor. This compound displays nanomolar affinity for the central cannabinoid receptor but is not active on the peripheral cannabinoid receptor. In vitro, SR141716A antagonises the inhibitory effects of cannabinoid receptor agonists on both mouse vas deferens contractions and adenylyl cyclase activity in rat brain membranes. After intraperitoneal or oral administration SR141716A antagonises classical pharmacological and behavioural effects of cannabinoid receptor agonists. This compound should prove to be a powerful tool for investigating the in vivo functions of the anandamide/cannabinoid system.

Neurotoxicology And Teratology • March 1994

Effect of prenatal marijuana exposure on the cognitive development of offspring at age three

Day NL1, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, Cornelius MD, Geva D.

1. Department of Psychiatry, University of Pittsburgh School of Medicine, PA

<http://www.ncbi.nlm.nih.gov/pubmed/8052191>

Marijuana is the most commonly used illicit substance among pregnant women. Although there has been substantial concern about the effects of substance use during pregnancy, few studies have assessed the effects of prenatal exposure to marijuana and even fewer have provided longitudinal data on the developmental outcome of offspring. This is a report from a longitudinal study of substance use during pregnancy. The women in the cohort were of lower socioeconomic status, most were single, half were white and half were African-American. Women were interviewed at the fourth and seventh prenatal months, and women and children were assessed at delivery, 8, 18, and 36 months. Pediatric assessment included physical and cognitive development. At each study phase, mothers were interviewed about life style, living situation, current substance use, sociodemographic, and psychological status. Findings are reported on 655 women and children who were assessed at the third year. There were significant negative effects of prenatal marijuana exposure on the performance of 3-year-old children on the Stanford-Binet Intelligence Scale. The effects were associated with exposure during the first and second trimesters of pregnancy. Among the offspring of white women, these effects were moderated by the child's attendance at preschool/day-care at age three.

Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study

Oviedo A1, Glowa J, Herkenham M.

Section on Functional Neuroanatomy, NIMH Bethesda, MD, USA

<http://www.ncbi.nlm.nih.gov/pubmed/6090910>

The active ingredient of marijuana is (-)-delta 9-tetrahydrocannabinol (delta 9-THC). delta 9-THC and other natural and synthetic cannabinoids such as CP-55,940 inhibit spontaneous activity and produce catalepsy in animals in a receptor-mediated fashion. Tolerance develops to the motor effects of delta 9-THC after repeated administration. To test the hypothesis that tolerance is mediated by changes in cannabinoid receptor binding characteristics, we used quantitative in vitro autoradiography of [3H]CP-55,940 binding to striatal brain sections from rats treated either chronically or acutely with delta 9-THC, CP-55,940, or the inactive natural cannabinoid cannabidiol. In the chronic conditions, rats were given daily i.p. injections of delta 9-THC (10 mg/kg), cannabidiol (10 mg/kg), or CP-55,940 (1, 3, or 10 mg/kg) for 2 weeks and sacrificed 30 min after the last injection. In the acute condition, animals received a single dose (10 mg/kg) prior to sacrifice. Rats developed tolerance to the inhibitory effects of delta 9-THC and CP-55,940, assayed in an open field on days 1, 7, and 14. Cannabidiol had no effect on behavior. Densitometry of [3H]CP-55,940 binding to brain sections showed that delta 9-THC- and CP-55,940-treated animals had homogeneous decreases in binding in all structures measured at the selected striatal levels. Cannabidiol had no effect on binding. Analysis of binding parameters showed that alterations in the acute condition were attributed to changes in affinity (KD), whereas the major changes in the chronic condition were attributed to a lowering of capacity (Bmax). The effects in the 1, 3, and 10 mg/kg CP-55,940 conditions were dose-dependent and paralleled the behavioral data showing that the animals given the highest dose developed the greatest degree of tolerance. The data suggest that tolerance to cannabinoids results at least in part from agonist-induced receptor down-regulation.

Community Dentistry And Oral Epidemiology • April 1993

Effects of cannabis smoking on oral soft tissues

Darling MR1, Arendorf TM.

1. Faculty of Dentistry, University of the Western Cape, Mitchells Plain, South Africa

<http://www.ncbi.nlm.nih.gov/pubmed/8485974>

The oral effects of cigarette smoking have been well documented but the effects of cannabis smoke on the oral environment have been poorly documented. Three-hundred cannabis/tobacco/methaqualone smokers were examined. Two control groups consisting of 152 tobacco- and 189 non-smokers respectively were examined similarly. Health of the oral tissues and oral dryness was recorded. Lesions present included leukoedema, leukoplakia and numerous others. The only significant differences between lesions and conditions noted in cannabis users and controls occurred with respect to leukoedema, dry mouth and traumatic ulcer.

The Medical Journal Of Australia • April 1992

The human toxicity of marijuana

Nahas G1, Latour C.

Department of Anesthesiology, College of Physicians and Surgeons, Columbia University

<http://www.ncbi.nlm.nih.gov/pubmed/1313532>

The pathophysiological effects of marijuana smoke and its constituent cannabinoids were reported first from in-vitro and in-vivo experimental studies. Marijuana smoke is mutagenic in the Ames test and in tissue culture and cannabinoids inhibit biosynthesis of macromolecules. In animals, marijuana or delta 9-tetrahydrocannabinol (THC), the intoxicating material it contains, produces symptoms of neurobehavioural toxicity, disrupts all phases of gonadal or reproductive function, and is fetotoxic. Smoking marijuana can lead to symptoms of airway obstruction as well as squamous metaplasia. Clinical manifestations of pathophysiology due to marijuana smoking are now being reported. These include: long-term impairment of memory in adolescents; prolonged impairment of psychomotor performance; a sixfold increase in the incidence of schizophrenia; cancer of mouth, jaw, tongue and lung in 19-30 year olds; fetotoxicity; and non-lymphoblastic leukemia in children of marijuana-smoking mothers.

Marijuana smoking: effect of varying delta 9-tetrahydrocannabinol content and number of puffs

Azorlosa JL1, Heishman SJ, Stitzer ML, Mahaffey JM.

1. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

<http://www.ncbi.nlm.nih.gov/pubmed/1313866>

The purpose of this study was to determine marijuana dose-effects on subjective and performance measures over a wider dosage range than previously reported using technology which allowed for specification of both the volume and delta 9-tetrahydrocannabinol (THC) content of smoke delivered, and to relate these effects to plasma THC levels. Seven male community volunteers, who were moderate users of marijuana, smoked 4, 10 or 25 puffs from cigarettes containing either 1.75 or 3.55% THC on 6 separate days. Postsmoking plasma THC levels were systematically related to both number of puffs and cigarette THC content. Maximal THC levels occurred immediately after smoking and ranged from 57 to 268 ng/ml. These plasma levels provided a measure of systemic delivery when a known volume and THC content of marijuana smoke was inhaled. Orderly dose-related increases were also observed for heart rate, expired air carbon monoxide and subjective report of drug effects. The 25-puff, 3.55%-THC condition produced greater plasma THC levels than previously reported and reliably impaired performance on a battery of psychomotor and cognitive tasks with substantial individual differences noted in the degree of performance impairment. Puff number/THC content combinations producing comparable plasma THC levels resulted in similar subjective effects and performance impairment. This study provided a comprehensive assessment of the pharmacological effects of smoked marijuana over a wider and more precisely controlled dosage range than has been accomplished previously.

Marijuana and Immunity

By Leo E. Hollister, M.D.

Full text with 43 references

http://www.marijuanalibrary.org/JOPD_Immunity_Hollister_92.html

Few areas of scientific research have been as controversial as the effect of marijuana on immune defenses. The effects of marijuana on health in general have been marked by polarities of belief or interpretation of evidence often due to the prejudices of investigators. In addition, evidence of altered immune functions is derived mainly from in vitro tests or ex vivo experiments, which employed doses of cannabinoids far in excess of those that prevail during social use of marijuana. Finally, the clinical significance of the experimental observations is difficult to assess.

The present review will attempt to objectively assess the evidence. Other recent reviews of the subject have also appeared, with varying degrees of intensity of coverage (Hollister 1986; Maykut 1985; Munson & Fehr 1983; Rosenkrantz 1976). For purposes of a more systematic discussion, immunity will be considered as several separate topics: (1) cell-mediated immunity, (2) humoral mechanisms, (3) cellular defenses, and (4) immunogenicity of marijuana or cannabinoids.

CELL-MEDIATED IMMUNITY **Lymphocyte Transformation**

Lymphocytes exposed to several mitogens divide rapidly, increase protein and nucleic acid synthesis, and show morphological changes resembling blasts. This test of the ability of T-lymphocytes to transform themselves measures one potential aspect of cell-mediated immunity. A direct way to measure the activation of lymphocytes is to measure the rate of incorpora-

tion of nucleic acid, such as 3H-thymidine, into the cells following addition of the mitogen to the culture. All studies are conducted in vitro.

An early study (Nahas et al. 1976) measured 3H-thymidine uptake in normal human lymphocytes stimulated by both phytohemagglutinin (PHA) and allogenic cell mixed lymphocyte culture (MLC). The incorporation of 3H-thymidine was equally inhibited by 10⁻⁵M to 10⁻⁴M concentrations of D9-tetrahydrocannabinol (THC), D8-tetrahydrocannabinol (D8-THC), their corresponding 11-OH metabolites, a variety of other inactive cannabinoids, and olivetol. THC in similar concentrations also depressed 3H-uridine uptake, indicating an effect of protein and RNA synthesis as well. These concentrations were 10 to 20 times greater than those reported earlier by the same group (Nahas et al. 1974) as having similar effects. In this study, cell-mediated immunity was evaluated in 51 young, chronic marijuana smokers whose lymphocytes were stimulated in vitro by PHA and MLC. As compared with normal controls, 3H-thymidine uptake was reduced.

Klein and colleagues (1985) added the predominantly T-cell mitogens, PHA and concanavalin A (Con A), and the B-cell mitogen, E. coli lipopolysaccharide (LPS), to mice spleen cells treated with varying concentrations of THC and its active metabolite 11-OH-THC. Both T-cell lymphocyte and B-cell lymphocyte proliferation in response to mitogens were suppressed by THC, but considerably less by 11-OH-THC. Proliferation of both types of lymphocytes was completely inhibited by concentrations of THC (10ug/ml) that were not directly lytic to the cells. Lower concentrations of THC were found to inhibit

B-cell lymphocytes than those required for T-lymphocytes, suggesting that humoral immunity was more impaired than cell-mediated immunity in this system.

By no means have all studies of cell-mediated immunity in marijuana smokers or in vitro exposure of T-cells to cannabinoids-often conducted in exactly the same way-shown evidence of immunosuppression. Indeed, the inconsistency of study findings has led to the present state of ambiguity.

White, Brin and Janicki (1975) obtained peripheral blood lymphocytes from 12 healthy long-term marijuana smokers. The blastogenic response to PHA and pokeweed mitogen were measured in vitro by ³H-thymidine uptake. The responses of lymphocytes from the marijuana smokers were not significantly different from those who did not smoke the drug.

Lau and colleagues (1976) observed eight chronic smokers of marijuana in a hospital setting over a 30-day period. Each subject received a placebo during the first six days, followed by THC in oral doses up to 210 mg/day for the next 18 days, then a placebo for the last six days. The response of their lymphocytes to PHA stimulation, as measured by ³H-thymidine uptake, was no different in either of the three periods.

Rachelfsky and Opedz (1977) stimulated normal human lymphocytes with PHA and with MLC, and ³H-thymidine uptake was measured. The uptake of thymidine was unchanged in lymphocytes exposed to 1.9×10^{-4} M or 12.0×10^{-4} M concentrations of THC. Higher concentrations of THC precipitated in the medium. Changes were comparable in cells exposed to THC and in those not so exposed.

Kaklamani and colleagues (1978) obtained peripheral lymphocytes from 12 chronic users of marijuana and 15 nonusing control subjects. Lymphocytes from the experienced marijuana users were obtained before and after smoking hashish. Incorporation of ¹⁴C-thymidine, after PHA stimulation

and formation of rosettes of sheep erythrocytes, was no different between the normal controls and the marijuana users either before or after the latter had smoked hashish.

Whatever immunosuppressive effects marijuana may have, they are not dependent on psychoactive components. A variety of cannabinoids, which have no apparent central nervous system activity, share an apparent immunosuppressive action (Smith et al. 1978).

T-Lymphocyte Rosette Formation

Another commonly used measure of cell-mediated immunity is the ability of T-lymphocytes to form in vitro rosettes of sheep erythrocytes surrounding T cells. A dose-related decrease in rosette formation was found in sensitized T cells exposed in vitro to various concentrations of THC in this medium (Cushman, Khurana & Hashim 1976). Cushman and Khurana (1977) tested 10 subjects during a four-week cycle of marijuana smoking, so that the subjects were exposed chronically rather than acutely, and the results showed a decrease in early T-cell formation, but no change in either late T-cell or B-cell rosettes. When Gupta, Grieco and Cushman (1974) compared 23 chronic marijuana smokers with 23 nonsmokers, T-cell rosettes were decreased in the users as compared with nonusers, but associated with B-lymphocytes were not different, suggesting a selective effect on cell-mediated immunity.

Petersen, Graham and Lemberger (1976) tested three subjects who smoked "street" marijuana for rosette formation and blastogenesis. Two of three showed decreased rosette formation and impaired blastogenesis following stimulation of their lymphocytes with PHA. In another trial, rosette formation was measured in six persons three to six hours after they smoked a marijuana cigarette containing 10mg of THC. Rosette formation was impaired in five of the subjects, and became normal 24 hours later in all but one subject. Thus, it appeared that the effects of marijuana on T-lymphocytes are vari-

able and reversible, suggesting that factors other than exposure to marijuana itself may be involved.

Mice immunized with sheep erythrocytes were treated with intraperitoneal doses of 10, 25, and 40mg/kg/day of THC for seven to eight days. Both plaque-forming and rosette-forming cells were decreased by the 25mg/kg/day dose (Lefkowitz et al. 1978). Monkeys were exposed to three levels of marijuana smoke over a six-month period. Plasma immunoglobulins (IgG and IgM) were decreased in those monkeys exposed to medium and high concentrations of smoke. In vitro tests by Dual and Heath (1975) of the response of lymphocytes to Con A were decreased. Thus, both humoral and cell-mediated immunity appeared to be affected. However, the authors asserted that it is impossible to assess the in vivo implications from tests of this sort.

Cushman and Khurana (1977) tested 10 subjects during a four-week cycle of marijuana smoking, so that the subjects were exposed chronically rather than acutely. The results showed a decrease in early T-cell rosette formation, but no change in either late T-cell or B-cell rosettes.

These studies also indicated that T-lymphocyte function, as measured by rosette formation, was decreased when the cells are exposed to cannabinoids either in vitro or ex vivo. However, these impairments were rapidly reversible.

Other Measurements of Cell-mediated Immunity

A number of other measurements of cell-mediated immunity have pointed in the same direction. Although both impaired allograft rejection and decreased hemagglutinin titers were found in animals treated with cannabinoids, the effect on allograft rejection as a measure of cell-mediated immunity was greater (Munson et al 1976). Susceptibility to infection with herpes simplex virus type 2 applied directly to the vagina was increased in mice

that had received doses of 100mg/kg/day of THC (Mishkin & Cabral 1985). A similar increased susceptibility was found in guinea pigs treated with doses of 4.0 and 10mg/kg/day (Cabral et al. 1986).

Morohan and colleagues assessed the LD50 dose of *Listeria monocytogenes* in mice treated with THC in doses of 38, 75 and 150mg/kg. The LD50 was decreased 10-, 17- and 657-fold by each dose, respectively. The marijuana extract was less active. A similar challenge with herpes simplex type 2 virus showed a 96-fold decrease following administration of marijuana extract. These situations are not at all comparable to human exposure.

The vast majority of people can be made sensitive to dinitrochlorobenzene (DNCB), a powerful skin sensitizer. DNCB is often used with "recall" antigens (eg. tuberculin and mumps) to test patients for anergy. Sensitivity to DNCB was found in all 34 chronic marijuana smokers who were tested as compared with 96 percent of 279 healthy nonsmokers. On the other hand, 384 patients with cancer, whose cell-mediated immunity is sometimes decreased, showed a positive reaction in only 70 percent of those tested (Silverstein & Lessin 1974). Such evidence raises questions about the clinical significance of experiments that have shown evidence of cell-mediated immunity from cannabinoids.

It has been hypothesized that the membrane-disordering effects of THC may affect the binding of antigens to cellular receptors, accounting for a decrease in cell-mediated immunity. On the other hand, the combination of increased membrane disorder and inhibition of acyltransferase activity in B cells and T cells could impair the transfer of cellular constituents (Baczynsky & Zimmerman 1983b). Regardless of whether the action is a nonspecific one at the cell membrane or at a more primary site, impaired immunity remains precisely that. However, a cell membrane site of action could explain the apparent transitory nature of the observed alterations in cell-mediated immunity, as well as the requirement for much larger concentrations of cannabinoids than those usually encountered during social use of marijuana.

Summary of Effects of Cell-mediated Immunity

In summary, the effects of cannabinoids on cell-mediated immunity are contradictory. Such evidence as has been obtained to support such an effort has usually involved doses and concentrations that are orders of magnitude greater than those obtained when marijuana is used by human subjects. Clinically, one might assume that sustained impairment of cell-mediated immunity might lead to an increased prevalence of opportunistic infections, or an increased prevalence of malignancy, as seen in the current epidemic of acquired immune deficiency syndrome (AIDS). No such clinical evidence has been discovered or has any direct epidemiological data incriminated marijuana use with the acquisition of human immunodeficiency virus infection or the clinical development of AIDS. Even though some degree of impairment of immune responses were to occur, the remaining immune function may be adequate, especially in the young persons who are major users of cannabis.

HUMORAL IMMUNITY Transformation of B-Lymphocytes

Transformation of B cells stimulated by the mitogen PLPS was inhibited more than were T cells stimulated by PHA following the same doses of THC in mice (Klein et al. 1985). This evidence of diminished B-cell reactivity following the administration of THC was confirmed in another study (Munson et al. 1976) that showed a dose dependent suppression from doses of 50, 100, and 200 mg/kg of THC in mice. These doses are enormous, of course.

Antibody Formation

A frequently used measure of humoral immunity is the ability of splenic lymphocytes from mice that are immunized against sheep erythrocytes to form plaques when exposed to in vitro to sheep erythrocytes. Levy and Heppner (1981) found that both THC and haloperidol produced dose-dependent

reductions in hemolytic plaque-forming cell (PFC) numbers at the time of peak reactivity (day 4) in control mice. Treatment with THC and haloperidol only delayed the time of peak PFC formation by 24 to 48 hours (doses were high enough to produce signs of gross behavioral toxicity). Neither THC nor other cannabinoids had any effect on the titer of serum hemagglutinating antibody measured seven days after immunization.

Baczynsky and Zimmerman (1983a) immunized mice with sheep erythrocytes on Day 1 (primary immune response) and on Days 1 and 28 (secondary immune response) and measured hemagglutinin titers. Mice treated with 10 mg or 15 mg of THC during the primary immunization period exhibited a suppression of the primary humoral immune response. These doses also suppressed the secondary immune response, even when given during the period of primary immunization. Mice treated with THC during the secondary immunization period showed no measurable response. Other cannabinoids had no effect.

Immature mice immunized with sheep erythrocytes also showed suppression of the immune response when treated with THC in doses of 1.0, 5.0, and 10.0 mg/kg. Splenic weight was reduced and PFC as well as hemagglutinin titers were lower than controls. The suppression was specific for THC and was not observed with cannabidiol or cannabitol, even at doses of 25 mg/kg (Zimmerman et al. 1977). Some evidence of tolerance or hyporesponsiveness to this humoral antibody suppression by THC was found when mice were treated with THC for five days prior to immunization as well as afterward (Loveless, Harris & Munson 1981-82).

Rosenkrantz, Miller and Esber (1975) immunized rats with a single intraperitoneal dose of sheep erythrocytes during, before and after administration of THC in order to determine its effect on the inductive and productive phases of the primary immune response. following a dose of 10 mg/kg, THC decreased the primary immune response 33 to 40 percent; the inductive phase was decreased by 48 to 78 percent by all doses of THC and the productive

phase was decreased by 26 to 59 percent by the higher doses.

The same group (Luthra et al. 1980) tested the primary immune response of rats to intraperitoneal administration of sheep erythrocytes after five to 26 days following pretreatment with THC in order to determine if tolerance developed to the immunosuppressant effects. As measured by splenic antibody-forming cells and hemagglutinin/hemolysin titers, no evidence of tolerance was found.

Summary of Effects of Humoral Immunity

In summary, humoral immunity, as tested by a number of in vitro procedures, seems also to be impaired by cannabinoids, but this effect was most evident for THC. The clinical significance of such changes is questionable due to the great concentrations of cannabinoids used and the lack of any epidemiological evidence of increased bacterial infections in chronic users of marijuana.

CELLULAR DEFENSES Leukocytes and Lymphocytes

When 10 subjects were followed through a four-week cycle of marijuana smoking, no change was observed in either peripheral leukocyte or absolute lymphocyte counts (Cushman & Khurana 1977). Leukocytes from five chronic marijuana smokers were compared with those from five nonusers of the drug for their ability to migrate after exposure to THC or marijuana extract. Both treatments inhibited leukocyte migration without killing the cells, both in cells from users and nonusers of marijuana. The prevailing THC concentration needed to accomplish this was 2.0ug/ml, a couple of orders of magnitude greater than any THC plasma concentrations usually found clinically (Schwartzfarb, Needle & Chavez-Chase 1974).

Natural Killer-cell Activity

Natural killer-cell activity in rats was decreased by subchronic treatment (25 days) with THC, but not after acute treatment (one day). This effect was not found in rats treated simultaneously with naloxone, suggesting possible involvement with the opiate system (Patel et al 1985). When injected into mice, both THC and its active metabolite 11-OH-THC suppressed splenic natural killer-cell activity in vitro. The tissue concentrations of the cannabinoids were reported as being 5.0-10.0 ug/ml, about two orders of magnitude greater than those that might be experienced during the social use of marijuana (Klein, Newton & Friedman 1987).

Macrophages

Macrophages work closely with T-cells as part of the immunological defense system. On glass surfaces, macrophage cultures normally show spreading, which is an indication of their mobility. The addition of THC to the medium inhibited the degree of spreading. It also inhibited the phagocytosis of yeast particles (Lopez-Cepero et al 1986). However, another experiment (Munson et al. 1976) using intact mice that were treated with a single dose or multiple doses of THC could not demonstrate impairment in reticuloendothelial activity, as measured by the intravascular clearance of colloidal carbon.

Summary of Effects on Cellular Defenses

It is somewhat surprising that newer techniques of cell sorting, which permit determination of absolute counts of T- and B-lymphocytes as well as subsets of T-lymphocytes, have not been utilized. The evidence from the in vitro studies is weakened by the high concentrations of drug that were used. Clinically, evidence for impairment of cellular defenses has not been forthcoming.

IMMUNOGENICITY OF CANNABINOIDS

Laboratory Studies

It has been hypothesized that THC, a relatively simple chemical, can act as a hapten and become an immunogen. If such were the case, tolerance to THC might be explained on an immunological basis as well as the rare reports of allergic reactions. Azathioprine, an immunosuppressant, had a modest effect in mitigating the hypotensive effects of THC in spontaneously hypertensive rats. Spleen cells from mice treated with THC showed slightly more blast transformation in culture than untreated spleen cells, either with or without THC being added to the culture medium. However, the degree of blast transformation was far less than that produced by PHA. This somewhat weak evidence for an immunogenic action of THC came from a laboratory that later stressed the immunosuppressant effects of marijuana (Nahas, Zugary & Schwartz 1973).

Watson, Murphy & Turner (1983) employed a technique used to test compounds for their potential for producing allergic contact dermatitis and that also maximizes the degree of skin sensitization of guinea pigs. Sensitivity was greatly increased by THC and cannabidiol, but less so with other cannabinoids.

Clinical Studies

In a clinical study conducted in the southwestern United States (Freeman 1983), skin tests were applied to 90 patients with various forms of atopy. The test was positive for 63 patients for marijuana pollen as compared to only 18 who reacted to tobacco leaf. However, it is unlikely that marijuana pollen contains many cannabinoids, but rather contains proteins that may be sensitizing.

A series of 28 marijuana smokers showed precipitins for *Aspergillus* antigens:

13 were positive as compared to one of 10 controls. Lymphocytes showed significant blastogenesis in three of those subjects who tested positive. Seven of these 23 subjects reported bronchospasm following the smoking of marijuana, and one patient had evidence of systemic aspergillosis (Kagen et al. 1983). As it is well known that marijuana contains contaminants, including molds and fungi, it is not surprising that these should cause allergic reactions in some users. The study does not indicate that cannabinoids themselves are immunogens.

Skin testing with cannabinoids seems to be useless for determining the rare patient with sensitivity to marijuana. A variety of intradermal tests with various cannabinoids and common allergens was applied to 63 marijuana users by Lewis and Slavin (1975). Two users, who were clearly atopic with a past history of bronchial asthma, also reported experiencing asthma after some exposures to marijuana. A third subject with a history of allergic rhinitis also experienced similar symptoms following marijuana use. All three of these subjects had negative skin tests to cannabinoids. On the other hand, seven subjects who tested positive for hemp and one who tested positive to D8-THC had no clinical manifestation of marijuana sensitivity.

A 29-year-old woman (known to be allergic to ragweed) experienced symptoms of anaphylactoid reaction that lasted 20 to 30 minutes immediately after smoking marijuana. Skin tests with THC showed a 2+ reaction, and with cannabidiol a 1+ reaction (Liskow, Liss & Parker 1971). The weakly positive skin tests do not necessarily indicate that the reaction was due specifically to cannabinoids.

Summary of Immunogenicity

While it is possible that a few persons may become truly allergic to cannabinoids, it is far more likely that allergic reactions, which have been exceedingly rare following the use of marijuana, are due to contaminants. Marijuana

is grown in the field and harvested along with everything else (eg., bacteria, fungi, molds, parasites, worms, chemicals) that may be found in such field plants. That such impure material, when smoked and inhaled into the lungs, causes so little trouble is really a marvel.

SUMMARY AND CONCLUSIONS

Despite the fairly large literature that developed during the past 15 years or so, the effect of cannabinoids on the immune system is still unsettled. The evidence has been contradictory and is more supportive of some degree of immunosuppression only when one considers in vitro studies. These have been seriously flawed by the very high concentrations of drug used to produce immunosuppression and by the lack of comparisons with other membrane-active drugs. The closer that experimental studies have been to actual clinical situations, the less compelling has been the evidence.

Although the topic was of great interest during the 1970s, as indicated by the preponderance of references from that period, interest has waned during the present decade. This waning of interest suggests that perhaps most investigators feel that this line of inquiry will not be rewarding. The AIDS epidemic has also diverted the attention of the immunologists to the far more serious problem of the truly devastating effects a retrovirus can have on a portion of the immune system.

The relationship between the use of social drugs and the development of clinical manifestations of AIDS has been of some interest, however. Persons infected with the virus but not diagnosed as AIDS have been told to avoid the use of marijuana and/or alcohol. This advice may be reasonable as a general health measure, but direct evidence that heeding this warning will prevent the ultimate damage to the immune system is totally lacking.

Effects of delta-9-tetrahydrocannabinol exposure on adrenal medullary function: evidence of an acute effect and development of tolerance in chronic treatments

Rodríguez de Fonseca F1, Fernández-Ruiz JJ, Murphy L, Eldridge JC, Steger RW, Bartke A.

Department of Biochemistry, Faculty of Medicine, Complutense University, Madrid, Spain

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Previous studies have shown that the secretion of several stress-related hormones can be altered by exposure to marijuana or its purified constituents. The purpose of this study was to examine changes in adrenal medullary function caused by acute, subchronic and chronic treatments with two different doses of delta-9-tetrahydrocannabinol (THC). Acute exposure to THC caused a significant decrease in the adrenal medulla contents of both norepinephrine (NE) and epinephrine (E) and a significant increase in the E/NE ratio. These effects were mainly observed with the highest dose of THC, but they were not accompanied by a statistically significant decrease in adrenal medulla tyrosine hydroxylase activity, the rate-limiting enzyme in the catecholamine (CA) synthesis. These effects disappeared after seven or fourteen days of a daily THC treatment, which suggests the development of tolerance to this drug. Analysis of plasma PRL, ACTH and corticosterone levels showed some THC-related changes in these hormones. THC-induced modifications in ACTH and corticosterone were not in parallel to the changes in the adrenal medulla function, whereas those effects of acute THC on PRL release were statistically correlated with decreases of CA contents following acute THC. In conclusion, acute exposure to THC caused an alteration in the adrenal medullary function, reflected by a fall in endogenous stores of both CAs which could influence the adrenal medullary response to stress situations. This acute effect of THC could be mediated by the pituitary secretion of PRL, although the possibility of an effect directly exerted on the adrenal medulla chromaffin cells should be also considered.

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Marihuana and mouth cancer

By G.A. Caplan

The Prince of Wales Hospital Randwick, NSW 2031, Australia

Full text is available as a scanned copy of the original print version

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293311/pdf/jrsocmed00123-0068b.pdf>

Boyle et al. in their review of the epidemiology of mouth cancer (November 1990 JRSM, p 724) made no mention of marihuana smoking as a risk factor. During the last 5 years there have been 13 reports of cancer of the mouth and larynx among chronic marihuana smokers in Australia and the United States. Five of the 13 had no other risk factors and all were young (<55 years old). The same literature search revealed only three reports of lung cancer amongst marihuana smokers.

This evidence suggests that marihuana smoking has a greater carcinogenic effect on the upper than the lower airways. If true this would correlate with respiratory function studies which demonstrate definite abnormalities in the proximal airways, but not in the peripheral airways. It has been hypothesized that the rapid, deep inhalation technique usually employed in smoking marihuana leads to earlier deposition of particulate material due to turbulence and inertial impaction. Whatever the reason, marihuana smoking as a possible cause of oral cancer deserves mention and further study.

Prenatal marijuana use: epidemiology, methodologic issues, and infant outcome

Day NL1, Richardson GA.

1. Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, PA

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What do we know about marijuana use among women of reproductive age and about the use of marijuana during pregnancy? Marijuana is the most commonly used illicit substance, and after alcohol and tobacco, the most commonly used drug during pregnancy. Women who use marijuana are more likely to be white, younger, and to use other substances. The characteristics of women who use marijuana during early pregnancy are similar, although women who continue to use marijuana throughout pregnancy are somewhat different. These women are less-well educated, of lower social class, much more likely to use other substances, and more likely to be black. We do not know why some women use marijuana while others do not, and why some women discontinue their use during pregnancy while others do not. What do we know about the effects of marijuana use during pregnancy? A number of studies have investigated the relationship between prenatal marijuana exposure and outcome at birth. The results, unfortunately, are equivocal. Prospective studies that have examined women at regular and frequent intervals during pregnancy, in general, have not found a relationship between marijuana use and birthweight (Day NL, Sambamoorthi U, Taylor P, et al: unpublished data, 1990) although some have reported a small effect of marijuana use on birth length (Day NL, Sambamoorthi U, Taylor P, et al: unpublished data, 1990). Other studies, some prospective and some retrospective, have reported correlations between marijuana use during pregnancy and smaller size at birth. Several of these studies, however, failed to control adequately for other illicit drug use while one used marijuana only as a dichotomous variable in the analysis. Therefore, we do not yet know whether there is or is not an effect of marijuana use during pregnancy on intrauterine growth retardation. Only a few studies have reported on growth outside the neonatal period, and these studies have not found a consistent effect of prenatal marijuana exposure. There are, however, too few reports to assume that this is definitive. Several studies reported a relationship between prenatal marijuana use and the gestational age of the infant. As with growth, however, other studies have not corroborated these findings. Similarly, two studies have noted an increase in morphologic abnormalities, although one of these did not have a control group for comparison. Most studies have reported finding no relationship with either minor or major morphologic abnormalities. At birth, investigators have assessed the relationship between prenatal marijuana exposure and neurobehavioral outcome. Again, the results are contradictory.

Cancer • September 1990

Marijuana smoking and carcinoma of the tongue. Is there an association?

Caplan GA1, Brigham BA.

1. Department of Medical Oncology Prince of Wales Hospital, Randwick, Australia

Full text with 15 references

There is considerable theoretical evidence that marijuana should be carcinogenic. However, most reviews have found no direct evidence of chronic marijuana smoking causing lung cancer. Some recent reports implicate marijuana smoking as a cause of cancer of the upper aerodigestive tract, though most of the subjects were exposed to other, possibly confounding, etiologic factors, namely tobacco and alcohol. We report two cases of squamous cell carcinoma of the tongue in men who chronically smoked marijuana but had no other risk factors. The totality of cases may point to a predilection of marijuana smoke for carcinogenesis in the upper aerodigestive tract. This correlates with nonmalignant effects and may be related to a different method of smoking marijuana compared with tobacco.

[http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(19900901\)66:5%3C1005::AID-CNCR2820660535%3E3.0.CO;2-H/abstract](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19900901)66:5%3C1005::AID-CNCR2820660535%3E3.0.CO;2-H/abstract)

Brain Research • April 1988

Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems

Landfield PW1, Cadwallader LB, Vinsant S.

Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC, USA

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Although cannabinoids exert strong effects on brain function, there have been no extensive analyses of the long-term effects of cannabinoids on mammalian brain structure. Consequently, we conducted quantitative light and electron microscopic studies on the brains of rats treated chronically with delta 9-tetrahydrocannabinol (THC) (5 X weekly for 8 months--approximately 30% of the life-span). In these studies, we found significant THC-induced changes in hippocampal structure: specifically, THC-treated animals exhibited decreased neuronal density and increased glial cell reactivity (i.e. an increase of cytoplasmic inclusions). In addition, we confirmed prior reports of THC-induced increases in adrenal-pituitary activity, since both adrenocorticotrophic hormone (ACTH) and corticosterone were elevated substantially during an acute stress. However, the animals appeared to be only minimally affected behaviorally by the doses used (highest dose: 8 mg/kg) and no effects of THC were observed on several ultrastructural variables, including synaptic density. The observed hippocampal morphometric effects of chronic THC are similar to apparent glucocorticoid-dependent changes that previously have been found to develop in rat hippocampus during normal aging. Given that cannabinoids and steroids are similar in chemical structure in several respects, therefore, the present results seem to raise the possibility that chronic THC exposure may alter hippocampal anatomical structure by interactions with, or mimicry of, adrenal steroid activity.

Drugs of abuse and virus susceptibility

Friedman H1, Klein T, Specter S, Pross S, Newton C, Blanchard DK, Widen R.

1. Department of Medical Microbiology and Immunology, University of South Florida, College of Medicine, Tampa 33612

<http://www.ncbi.nlm.nih.gov/pubmed/2840802>

It is widely recognized that various microorganisms including viruses have immunomodulatory effects and, under appropriate circumstances, may markedly suppress the immune response mechanisms. Cannabinoids present in marijuana also have immunomodulatory effects. In the present studies THC as well as its metabolic product 11-OH THC were studied in regard to their effects in vivo and in vitro on selected parameters of the immune response system known to be important in antiviral resistance, including immunity to retroviruses. Cannabinoids markedly suppressed the ability of murine macrophages to spread on glass (an important functional marker of macrophages) as well as to phagocytize yeast particles. Splenic macrophage cultures treated with the cannabinoids also were deficient in their ability to produce interleukin 1 on appropriate stimulation with bacterial LPS. Spleen cells capable of producing antibody to sheep erythrocytes when stimulated with this antigen in vitro were markedly affected when treated with graded doses of THC or 11-OH THC. Furthermore, the blastogenic responsiveness of normal mouse splenocytes to the T-cell mitogens Con A and PHA as well as the B-cell mitogen E. coli LPS was markedly suppressed by graded concentrations of the cannabinoids in doses that did not affect the viability of the cells. Natural killer cell activity of normal mouse spleen cells was also markedly inhibited by THC and 11-OH THC. Similarly, these cannabinoids suppressed the blastogenic responsiveness and NK activity of human peripheral blood leukocytes from normal individuals. The ability of mouse spleen cells to produce interferon on in vitro stimulation was also suppressed by THC. In addition, injection of THC into mice suppressed blastogenic responsiveness of spleen cells, NK activity, and the production of interferon by lymphoid cells. Thus, it was apparent that these cannabinoids had immunomodulatory effects, both in vivo and in vitro, at noncytotoxic small doses and impaired the ability of the lymphoid cells to express immune function necessary for antiviral resistance.

Journal Of Psychoactive Drugs • January 1988

Cannabis 1988. Old drug, new dangers. The potency question

Mikuriya TH1, Aldrich MR.

Fitz Hugh Ludlow Memorial Library, San Francisco, California

<http://www.ncbi.nlm.nih.gov/pubmed/3292744>

Observation of the real world of social marijuana use, where autotitration is the norm, renders the scare tactics of the new marijuana proponents not only inaccurate but irrelevant. There is much published evidence about the availability of highly potent varieties of cannabis from the nineteenth century through the present day. The effects attributed to the new marijuana are the same ones debated for centuries in many different cultures. The assertion that "all marijuana research to date has been done on 1 or 2 percent THC material" (Cohen 1968) ignores several thousand years of human experience with the drug. The old medical cannabis extracts were stronger than most of the forms now available, though the potency of illicit hash oils by the mid-1970's was approaching the level of medicinal preparations available before their removal from the USP. While it may be true that sinsemilla is more widely available than 10 or 15 years ago, its potency has not changed significantly from the 2.4 to 9.5 percent THC materials available in 1973-1974 (see Table I), or the five to 14 percent sinsemilla of 1975 (Perry 1977). The range of potencies available then (marijuana at 0.1% to 7.8% THC, averaging 2.0% to 5.0% THC by 1975) was approximately the same as that reported now. With such a range, the evidence simply cannot support the argument by Cohen (1986) that marijuana is "ten or more times more potent than the product smoked ten years ago." And to say that marijuana potency has increased 1,400 percent since any date in history is patent nonsense.

Cannabinoids induce incomplete maturation of cultured human leukemia cells

Murison G, Chubb CB, Maeda S, Gemmell MA, Huberman E.

Full text with 25 references

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC298868/>

Monocyte maturation markers were induced in cultured human myeloblastic ML-2 leukemia cells after treatment for 1-6 days with 0.03-30 microM delta 9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana. After a 2-day or longer treatment, 2- to 5-fold increases were found in the percentages of cells exhibiting reactivity with either the murine OKM1 monoclonal antibody or the Leu-M5 monoclonal antibody, staining positively for nonspecific esterase activity, and displaying a promonocyte morphology. The increases in these differentiation markers after treatment with 0.03-1 microM THC were dose dependent. At this dose range, THC did not cause an inhibition of cell growth. The THC-induced cell maturation was also characterized by specific changes in the patterns of newly synthesized proteins. Pronounced among these changes was an increase in the synthesis of at least 10 proteins that are found abundantly in monocytes. The THC-induced differentiation did not, however, result in cells with a highly developed mature monocyte phenotype; the THC-treated cells failed to exhibit other monocyte markers such as attachment to the surface of tissue culture dishes or morphological maturation beyond the promonocyte stage. However, treatment of these "incompletely" matured cells with either phorbol 12-myristate 13-acetate or 1 alpha,25-dihydroxycholecalciferol, which are inducers of differentiation in myeloid leukemia cells (including ML-2 cells), produced cells with a mature monocyte morphology. Two other cannabinoids, cannabidiol and cannabitol, which were more cytotoxic than THC at comparable doses, also caused an increase in the expression of maturation markers, but at doses higher than those required for THC. The ML-2 cell system described here may be a useful tool for deciphering critical biochemical events that lead to the cannabinoid-induced "incomplete" cell differentiation of ML-2 cells and other related cell types. Findings obtained from this system may have important implications for studies of cannabinoid effects on normal human bone-marrow progenitor cells.

Effects of delta 9-THC, the principal psychoactive component of marijuana, during pregnancy in the rhesus monkey

Asch RH, Smith CG.

<http://www.ncbi.nlm.nih.gov/pubmed/3025441>

The effect of delta 9-tetrahydrocannabinol (THC), the principal psychoactive component in marijuana, was studied in pregnant and lactating rhesus monkeys. THC (2.5 mg/kg/d) or vehicle was administered during different periods of gestation, and effects on pregnancy outcome and hormone concentrations during pregnancy were studied. The most obvious effects were observed with administration early in pregnancy; three of five pregnancies aborted within days after the drug injections began, and one pregnancy resulted in a stillbirth at term. The three abortions were associated with a rapid decrease in chorionic gonadotropin and a subsequent fall in progesterone concentrations to nondetectable levels. In the two pregnancies that continued until term, estradiol concentrations were significantly higher than in vehicle control pregnancies. Daily THC administration during the middle or third portion of gestation resulted in lesser pregnancy loss (one premature birth and four live births at term with THC treatment during the middle portion; two premature births and three live births at term with THC treatment during the third portion). All the premature infants died within two weeks of birth. The weights of the infants at birth and weaning were not significantly different for the infants from vehicle control pregnancies and for full-term infants exposed to THC during gestation. Also, no effects on intrauterine growth and development were detected with ultrasound in the drug-treated pregnancies. With acute administration, THC readily crossed the placenta at term in rhesus monkeys and was transferred into the milk of nursing mothers. Significant blood levels of THC and depressant effects were observed in both mothers and neonates when the drug was administered to the mothers one hour before birth or during lactation.

Health aspects of cannabis

By L.E. Hollister

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Marijuana seems firmly established as another social drug in Western countries, regardless of its current legal status. Patterns of use vary widely. As with other social drugs, the pattern of use is critical in determining adverse effects on health. Perhaps the major area of concern about marijuana use is among the very young. Using any drug on a regular basis that alters reality may be detrimental to the psychosocial maturation of young persons. Chronic use of marijuana may stunt the emotional growth of youngsters. Evidence for an amotivational syndrome is largely based on clinical reports; whether marijuana use is a cause or effect is uncertain. A marijuana psychosis, long rumored, has been difficult to prove. No one doubts that marijuana use may aggravate existing psychoses or other severe emotional disorders. Brain damage has not been proved. Physical dependence is rarely encountered in the usual patterns of social use, despite some degree of tolerance that may develop. The endocrine effects of the drug might be expected to delay puberty in prepubertal boys, but actual instances have been rare. As with any material that is smoked, chronic smoking of marijuana will produce bronchitis; emphysema or lung cancer have not yet been documented. Cardiovascular effects of the drug are harmful to those with preexisting heart disease; fortunately the number of users with such conditions is minimal. Fears that the drug might accumulate in the body to the point of toxicity have been groundless. The potential deleterious effects of marijuana use on driving ability seem to be self-evident; proof of such impairment has been more difficult. The drug is probably harmful when taken during pregnancy, but the risk is uncertain. One would be prudent to avoid marijuana during pregnancy, just as one would do with most other drugs not essential to life or well-being. No clinical consequences have been noted from the effects of the drug on immune response, chromosomes, or cell metabolites. Contamination of marijuana by spraying with defoliant has created the clearest danger to health; such attempts to control production should be abandoned. Therapeutic uses for marijuana, THC, or cannabinoid homologs are being actively explored. Only the synthetic homolog, nabilone, has been approved for use to control nausea and vomiting associated with cancer chemotherapy.

Health Aspects of Cannabis

By L.E. Hollister

Full text with 185 references

<http://druglibrary.org/schaffer/hemp/medical/hollisterhealth.htm>

The modern era of research into the effects of cannabis in man began less than 20 years ago. Many issues about its health hazards, as they are with all drugs, remain controversial and ambiguous. Many adverse reactions to drugs were not recognized until after much exposure had occurred. Often these are idiosyncratic or allergic reactions. On the other hand, adverse reactions due to the extensions of the pharmacological action of a drug may be recognized both early and late. A similar pattern holds for cannabis.

The ambiguity currently surrounding the health hazards of cannabis may be attributed to a number of factors besides those which ordinarily prevail. First, it has been difficult to either prove or disprove health hazards in man from animal studies. When such studies of cannabis reveal possible harmful effects, the doses used are often large and the treatment is generally short. Second, cannabis is still used mainly by young persons in the best of health. Fortunately, the pattern of use is more often one of intermittent rather than regular use, the doses of drug usually being relatively small. This factor might lead to an underestimation of the potential impact of cannabis on health. Third, cannabis is often used in combination with tobacco and alcohol, among licit drugs, as well as a variety of other illicit drugs. Thus, potential health hazards from cannabis may be difficult to distinguish from those of concomitantly used drugs. Finally, the whole issue of cannabis use is so laden with emotion that serious investigations of health hazards of the drug have been colored by the prejudices of the experimenter, either for or against the drug as a potential hazard to health.

Assessment of the therapeutic potentials of marijuana is also clouded by prejudices, either for or against the drug. Virtually every claim of therapeutic benefit made for marijuana is for a condition for which there are already many effective treatments. Thus, to justify the use of the new agent, it must be subjected to the same elements of proof as a brand-new drug. Thus far, none of the potential indications has been officially recognized.

This report will focus on three main areas: (a) acute and chronic effects of cannabis in humans; (b) issues regarding its possible adverse effects on health, including its effects on driving ability; and (c) the therapeutic potential of cannabis constituents or synthetic homologs of such constituents.

II. Acute and Chronic Effects of Cannabis in Humans A. Acute Studies

The availability of synthetic trans-delta-9-tetrahydrocannabinol (THC), the major component of cannabis, and the chemical techniques for quantifying its content in cannabis preparations and in blood have made possible for the first time pharmacological studies which provide some precision in dose. When the material is smoked, as it is most commonly used in North America, a variable fraction of THC is lost by smoke escaping into the air or exhaled from the respiratory dead space. Relatively little is lost by pyrolysis, since it is likely that the cannabinoid is volatilized in advance of the burning segment of the cigarette. The efficiency of the delivery of a dose by smoking has been estimated to be about 18%, but frequent smokers obtain 23%, while infrequent users obtain only 10% (110). THC and marijuana extracts are also active by mouth; the systemic bioavailability of oral administration is only about 6%, one-third that from smoking (130).

When smoked, THC is rapidly absorbed, and effects appear within minutes. If marijuana is of low potency, effects may be subtle and brief. Seldom do they last longer than 2 to 3 h after a single cigarette, although users prolong the effects by repeated smoking. Oral doses delay the onset of symptoms for 30 min to over 2 h, as well as prolonging the span of action of the drug. These time schedules are consistent with knowledge of the pharmacokinetics of the drug. Smoking is similar to i.v. ad-

ministration in producing maximum plasma concentrations early, while p.o. administration produces slower rises of maximum plasma concentrations, which are also lower than those for smoking (105, 130). Although the route of administration affects the time course and the intensity of cannabis effects in man, the pattern of these effects was well established by early investigators (84, 88).

All observers have commented on the constant increase in pulse rate, often one of the first effects of the drug. Blood pressure tends to fall slightly or remains unchanged; at higher doses, orthostatic hypotension occurs. Conjunctival reddening is also consistently observed. Both this symptom and the increased pulse rate correlate quite well in time with the appearance and duration of psychic effects of the drug, as well as the plasma concentrations of the drug (6). Muscle strength is decreased. Appetite is consistently augmented, along with an increased food intake (80). Observed physiological effects have not included changes in pupil size, respiratory rate, or deep tendon reflexes.

Perceptual and psychic changes are biphasic. An initial period of euphoria or "high" is followed by drowsiness. Time sense is altered, hearing is less discriminant, and vision is apparently sharper with many visual distortions. Depersonalization, difficulty in concentrating and thinking, dreamlike states are prominent. Many of these symptoms are similar to those produced by psychotomimetics.

The effects that users derive from cannabis are extremely variable. Some of this variability depends on individual variation in degree of tolerance to the drug, based on prior use. Although it is customary to ascribe some variability to difference in setting, i.e., the type of conditions and surroundings which prevail during the drug use, or to set, i.e., the expectations of the user, proving the effects of either has been difficult. One study indicated that, with pharmacologically active doses of the drug, extreme variations in setting produced little alteration of drug effects, which were clearly different from those produced by placebo (82).

B. Chronic Studies

The effects of chronic use of cannabis are more to the point when considering the issues of its status as a possible social drug. Three largescale field trials of cannabis users have been implemented, but the results of these trials have done little to

allay apprehensions about the possible ill effects of chronic use. Objections have been made about the small samples used, the sampling techniques, and the adequacy of the studies performed.

Jamaica is a country in which cannabis is widely used, under the name ganja. The content of THC in native cannabis is generally high, estimated at severalfold that of cannabis generally supplied to users in North America. The average Jamaican user smokes seven to eight cannabis cigarettes a day, such use not being considered deviant in that country. Sixty adult workers, all men, were selected for study. Thirty were ganja smokers, and thirty were not, although the latter may have used cannabis tea. Extensive studies in the hospital revealed no significant physical abnormalities between the two groups. The smokers were found to be at greater risk of functional hypoxia, which might have been due to the fact that tobacco was also used by this group. Smokers claimed to use cannabis to work better, but evidence in a selected subgroup supported slightly decreased performance. The small sample and the fact that impairment may be difficult to detect in unskilled workers make it difficult to be sanguine about these generally negative results (147).

A similar study was done in Costa Rica, another country in which cannabis use is prevalent. Two groups of 80 subjects, users and nonusers, were compared by a variety of clinical and laboratory examinations. Essentially no difference between the two groups was detected (34). Fortyseven chronic users of hashish in Greece were compared with 40 nonusers, focussing primarily on tests of brain damage. No evidence of abnormality in function as judged by a variety of tests could be detected in the hashish group as compared with the others. The hashish users had a higher prevalence of personality disorders, probably unrelated to their use of hashish but possibly contributing to it (49).

If field studies fail to provide evidence of harm from prolonged use of cannabis, it is unlikely that experimental studies will do better, and such has been the case. The results of a 30day highdose cannabis study in which doses up to 210 mg of THC per day were administered p.o. to volunteers were most remarkable in how well the subjects tolerated such large doses (93). Tolerance was probably present in most subjects prior to the study, but it was rapidly augmented during it. Under these conditions, a mild withdrawal reaction was found when the drug

was abruptly discontinued. Additional unanticipated findings were weight gain, bradycardia, and an absence of psychotomimetic effects. As the amount of drug absorbed from p.o. administration may be small, these results are only partially applicable to smoking.

A longer experimental study in which cannabis was smoked rather than taken p.o. exposed subjects from 35 to 198 mg of THC daily for 78 days. The unique contribution of this study was the discovery of the effects of cannabis in lowering intraocular pressure. Other effects noted were lowering of serum testosterone levels, airway narrowing after heavy use, lack of chromosomal alteration, and unchanged immune responses (35). Other effects of chronic cannabis use are related in a specific publication of the New York Academy of Sciences on chronic cannabis use (31).

In summary, we have a very good idea of the acute effects of cannabis, although these are tempered by the dose of THC, the route of administration of the previous exposure of the user to the drug, and possibly by their past experiences with it. The effects of chronic use are somewhat less certain. Experimental studies suggest that tolerance develops rapidly, that a mild withdrawal reaction may occur, and that some acute effects may be reversed (for instance, a slow heart rate with chronic use rather than a rapid one as seen with acute use). Field studies have failed to detect any major health consequences from chronic heavy use of cannabis, but these studies have many deficiencies, most studies being far too small to pick up unusual or rare consequences that could be of great importance. Nonetheless, one is forced to conclude that cannabis is a relatively safe drug as social drugs go. To date it compares favorably with tobacco and alcohol, if not caffeine. One should bear in mind, however, the very long time that it took to determine the ill effects of these accepted social drugs.

III. Possible Adverse effects of Cannabis on Health

A. Immunity

A number of in vitro studies, using both human and animal material, suggest that cell-mediated immunity may be impaired after exposure to cannabis. Clinically, one might assume that sustained impairment of cell-mediated immunity might lead to an increased prevalence of malignancy, as seen in the current epidemic

of acquired immune deficiency syndrome (AIDS). No such clinical evidence has been discovered. Despite some degree of impairment of immune responses, the remaining immune function may be adequate, especially in the young person who are the major users of cannabis.

An impairment of cellular immunity in 51 chronic users of cannabis was shown by inhibition of lymphocyte blastogenesis from mitogen, phytohemagglutinin (171). A decrease in Tlymphocytes was found in 9 of 23 chronic cannabis users, employing rosette formation as a way of quantifying Tlymphocytes; the number of total lymphocytes was not different from nonusers (66). Thus, two early studies suggested that Tlymphocytes might be decreased in number as well as in ability to respond to an immunologic challenge. immunosuppression was shown in animals by prolonged allogenic skin graft survival, inhibited primary antibody production to sheep erythrocytes, and a diminished blastogenic response (109).

Further studies have tended to confirm an immunosuppressant action of cannabis in animals, whether the material was given p.o. or injected i.p. (144, 185). Mice treated with THC and challenged with gramnegative bacteria showed enhanced susceptibility (19). However, others using in vitro techniques for studying lymphocytes, have found no alteration in nucleic acid synthesis in the presence of as much as 10.6×10^{-4} M concentrations of THC (137).

Effects of cannabis on Tcells may be transitory. Smoking of cannabis temporarily decreased Tcell function in 13 chronic users as compared with 9 matched nonsmokers, but the effects varied from subject to subject and were closely related to the time the blood samples were drawn (134). Although early Tcell rosette formation was impaired in ten chronic cannabis smokers, despite a normal total of circulating Tcells, the absence of clinical evidence of greater disease susceptibility among such subjects makes this observation of dubious clinical importance (45, 126).

Other studies cast doubt on some of the earlier positive observations of impaired cellular immunity. Dinitrochlorobenzene is used as a skin test for intact delayed hypersensitivity, mediated by cellular immunity. No differences were observed in 34 chronic marijuana smokers as compared with 279 nonsmokers (152). The response of cultured lymphocytes from 12 longterm smokers of cannabis to two mitogens was not impaired as contrasted with lymphocytes from nonsmokers

(178). Even the ingestion of cannabis in amounts of 210 mg daily of THC failed to alter the response of the subjects lymphocytes to mitogen stimulation (103).

In summary, evidence is difficult to interpret concerning a possible suppressant effect of cannabis on cell-mediated immunity. If suppression occurs, it may only be transient, in the sense that recovery can occur. Further, the degree may not be clinically significant as the reserve capacity of the body to respond to immune challenge may not be exceeded. We simply do not know how much impairment is necessary to make someone vulnerable. Clinical experience has not yet indicated an increased vulnerability of cannabis users, but further observations of the possible contribution of marijuana use to the susceptibility to develop AIDS must be awaited.

B. Chromosomal Damage

Adverse effects on chromosomes of somatic cells have been especially controversial. The techniques of human cytogenetic studies still leave much to be desired. Assessing damage to chromosomes is more of an art than a science. Interpretations are highly subjective, and it is often difficult to get agreement between any two readers of the same slide. Further, processing of cells to make chromosomal preparations may differ from one laboratory to another, so that it is possible to get conflicting results from the same specimen even when read by the same reader. One needs only recall the controversy about chromosomal damage from lysergic acid diethylamide (LSD) a few years ago to interpret any reports of chromosomal damage with great caution. As similar types and degrees of chromosomal alteration have been reported in association with other drugs commonly used in medical practice, without any clinical evidence of harm, the significance of such changes remains unclear. Early reports were positive, but more recent reports were negative. A significant increase (3.4 versus 1.2%) of chromosomal abnormalities was reported in marijuana users as compared to nonusers (155). Changes were largely breaks or translocations of chromosomes. More of the latter were found in chronic cannabis users than in nonusers, but when breaks were included in the counts, the differences vanished (76). No increase in chromosomal breaks was found in cells from subjects taking p.o. hashish extract (which contains THC as well as cannabidiol), marijuana extract (containing only THC) or synthetic THC (128). After 72 days of chronic smoking of cannabis, no increase in break frequency was found over that which existed prior to the study (116).

Both the retrospective and prospective studies have flaws, and one simply cannot conclude that the issue is settled. For that matter, it has not yet been settled for a variety of drugs, including aspirin, in which an increased number of chromosomal abnormalities have been described. One must conclude for the time being that, even if a small increase in chromosomal abnormalities is produced by cannabis, the clinical significance is doubtful.

C. Pregnancy and Fetal Development

This is another area of great uncertainty about the meaning of data. Virtually every drug that has been studied for dysmorphogenic effects has been found to have them if the doses were high enough, if enough species are tested, or if the treatment is prolonged. The placenta is not a barrier to the passage of most drugs, so the assumption should be made that they will reach the fetus if taken during pregnancy (3).

This assumption is well validated for THC, based on autoradiographic studies (87). A high incidence of stunting of fetuses was seen in mice treated on day 6 of pregnancy with a single i.p. dose of 16 mg of cannabis resin per kg. No reduction in litter size or apparent malformations were seen. When the same dose was given repeatedly from days 1 to 6 of pregnancy. Fetal resorption was complete (133). Treatment of mice from days 6 to 15 of gestation with THC doses of 5, 15, 50, and 150 mg/kg had no effect on fetal weight, prenatal mortality rate, and frequency of gross external, internal, or skeletal abnormalities (50). Exposure of pregnant rats to either cannabis smoke or smoke from extracted marijuana throughout the gestation produced less fertile offspring with smaller reproductive organs in cannabis treated animals (12, 54).

Pregnant rabbits treated p.o. with daily doses of THC at 15 mg/kg on days 6 to 18 of gestation delivered infants without visible abnormalities (36). Injection s.c. of doses of THC up to 100 mg/kg daily on days 6 to 15 of gestation had no teratogenic effect (97). Fetal resorption was seen in rats treated with s.c. doses of THC at 100 mg/kg for days 1 to 20 of gestation, but lesser doses had no effect (18).

Clinical studies have also not elucidated the question. An epidemiological study found more meconium staining of the fetus and more disturbances of the dura-

tion of labor (either short or long) among 35 users of marijuana as compared to 36 nonusers (63). However, no significant difference was found between 19 moderate to heavy users and many more nonusers in regard to several neonatal outcomes (53). Small sample sizes reduce the confidence of results of either study. A much larger study involved 12,424 women of whom 1,246 (11%) were marijuana users. Lower birth weights, a shorter gestation period, and more major malformations were found among the offspring of users (111). No changes in serum human chorionic gonadotropin, placental lactogen, progesterone, estradiol, and estriol were found in 13 women who smoked marijuana during pregnancy, compared with a matched control number who did not (20).

In summary, it is still good practice in areas of ignorance, such as the effects of drugs on fetal development, to be prudent. While no definite clinical association has yet been made between cannabis use during pregnancy and fetal abnormalities, such events are likely to be rare at best and could be easily missed. The belated recognition of the harmful effects on the fetus of smoking tobacco and drinking alcoholic beverages indicates that some caution with cannabis is wise.

D. Cell Metabolism

Information currently available for the effect of cannabis on cell physiology and metabolism is limited. Smoke from both cannabis and tobacco increased the size of cytoplasm, nuclei, and nucleoli along with an increase in DNA content of human lung cell explants. Mitotic abnormalities were also noted with an increase of 10 to 25% over those of controls. Combination of both smokes produced greater abnormalities than either one alone. Malignant cell transformation of hamster lung culture was observed after administration of both types of smoke (108). These findings suggest that cannabis smoke is harmful to lung cells in cultures and contributes to the development of premalignant and malignant lesions.

Cannabinoids may also interfere with the normal cell cycle. Experiments with protozoan, *Tetrahymena*, synchronized in culture, showed a reduction in growth rate during log phase and lengthening of the mean division time upon exposure of THC. These changes were dose dependent (183). Addition of THC to various human and animal cell cultures has been shown to decrease synthesis of DNA. The clinical implication of some of these findings is obscure. On the one hand, expo-

sure to smoke from cannabis may be carcinogenic. On the other, the changes in nucleic acid synthesis, were they to be specific for rapidly dividing cells, such as those of malignancies, might be useful therapeutically in their treatment.

E. Psychopathology

Cannabis may produce directly an acute panic reaction, a toxic delirium, an acute paranoid state, or acute mania. Whether it can directly evoke depressive or schizophrenic states, or whether it can lead to sociopathy or even to "amotivational syndrome" is much less certain. The existence of specific cannabis psychosis, postulated for many years, is still not established. The fact that users of cannabis may have higher levels of various types of psychopathology does not infer a casual relationship. Indeed, the evidence rather suggests that virtually every diagnosable psychiatric illness among cannabis users began before the first use of the drug. Use of alcohol and tobacco, as well as sexual experience and "acting out" behavior, usually antedated the use of cannabis (68). When the contributions of childhood misbehavior, school behavioral problems, and associated use of other illicit drugs were taken into account, it was difficult to make a case for a deleterious effect of regular cannabis use (69). Thus, it seems likely that psychopathology may predispose to cannabis use rather than the other way around.

1. Acute panic reaction. This adverse psychological consequence of cannabis use is probably the most frequent. About one in three users in one high school and one in five in another reported having anxiety, confusion, or other unpleasant effects from cannabis use. These unpleasant experiences were not always associated with unfamiliarity with the drug; some subjects experienced these adverse reactions after repeated use (7). The conventional wisdom, however, is that such acute panic reactions occur more commonly in relatively inexperienced users of cannabis, more commonly when the dose is larger than that to which users may have become accustomed, and more commonly in older users who may enter the drug state with a higher level of initial apprehension (67).

The acute panic reactions associated with cannabis are similar to those previously reported to be caused by hallucinogens. The subject is most concerned about losing control or even of losing his or her mind. Reactions are usually self-limited and may respond to reassurance or "talking down"; in the case of cannabis use,

sedatives are rarely required as the inherent sedative effect of the drug, following initial stimulation, often is adequate. Occasionally one may see a dissociative reaction, but this complication is readily reversible. Depersonalization may be more longlasting and recurrent, somewhat akin to "flashbacks" reported following hallucinogens; the electroencephalogram shows no abnormality (158).

2. Toxic delirium. Very high doses of cannabis may evoke a toxic delirium, manifested by marked memory impairment, confusion, and disorientation (120). This nonspecific adverse psychological effect is seen with many drugs, but the exact mechanism is not clear in the case of cannabis as it is in the case of Datra stramonium smoking, for instance, which produces potent anticholinergic actions. As high doses of any drug tend to prolong its action, delirium is selflimited and requires no specific treatment. Highly potent preparations of cannabis are not as readily available in North America as in other parts of the world, so these reactions are less commonly observed in the United States and Canada.

3. Acute paranoid states. It is difficult to gauge the frequency of these reactions. In a laboratory setting, they are frequently encountered. Quite possibly the experimental setting creates a paranoid frame of reference to begin with. That this reaction is not peculiar to the laboratory is evident from reports in which it has been experienced in social settings (96). The illegal status of the drug might contribute in such instances, for while intoxicated, one might be more fearful of the consequences of getting caught. Undoubtedly, the degree of paranoia of the individual is also an important determinant, so that this reaction may represent an interplay between both the setting in which the drug is taken as well as the personality traits of the user.

4. Psychoses. A variety of psychotic reactions have been ascribed to cannabis use. Many are difficult to fit into the usual diagnostic classifications. Two cases of manic reaction were reported in children who were repeatedly exposed to cannabis by elders. Both required treatment with antipsychotic drugs but ultimately showed a full recovery (16). Hypomania, with persecutory delusions, auditory hallucinations, withdrawal, and thought disorder, was observed in four jamaican subjects who had increased their use of marijuana (71). Twenty psychotic patients admitted to a mental hospital with high urinary cannabinoid levels were compared with 20 such patients with no evidence of exposure to cannabis. The former group

was more agitated and hypomanic but showed less affective flattening, auditory hallucinations, incoherence of speech, and hysteria than the 20 matched control patients. The cannabis patients improved considerably after a week, while the control patients were essentially unchanged (146). Thus, a selflimiting hypomanic-schizophreniclike psychoses following marijuana has been documented.

Psychoses in a group of East Indian marijuana users were predominantly instances of toxic delirium, but those who had "schizoid" features became overtly schizophrenic during the period of intoxication (30). The aggravating effect of marijuana on preexisting schizophrenia has been documented (169). However, it was impossible to distinguish retrospectively those individuals who exhibited behavioral changes in association with marijuana smoking from those who did not (114).

A controversial clinical report of 13 adults with psychiatric disorder associated with the use of cannabis included some who had schizophreniclike illnesses and one with depressive features. The majority of these subjects had only used cannabis, which was thought to be the major precipitant of their disorders (98). A similar report from South Sweden involved 11 patients observed over a 1 year period. None had previous psychosis or abused other drugs. A mixture of affective and schizophreniclike symptoms, as well as confusion and pronounced aggressiveness was observed. The mental disturbances were self-limiting and rare (132).

It is impossible to think of any controlled trial that could be designed to detect adverse psychiatric effects from chronic use of a drug. Thus, clinical reports have long served as the surest way to detect adverse effects of both social and medically used drugs. Imperfect as such reports are, they can never be ignored.

Chronic use of hashish among a group of military personnel was tolerated quite well. Panic reactions, toxic psychosis, and schizophrenic reactions were infrequent occurrences among this group of 720 smokers, except when hashish was used in conjunction with alcohol or other psychoactive drugs. Rather, these 110 subjects who used the highest doses (over 50 g/month) developed a chronic intoxicated state characterized by apathy, dullness, lethargy, as well as impaired judgement, concentration, and memory (163).

The paranoid psychosis associated with longterm cannabis use was contrasted

with paranoid schizophrenia in groups of 25 Indian patients with each syndrome. The cannabis psychosis was characterized by more bizarre behavior, more violence and panic, an absence of schizophrenic thought disorder, and more insight than was seen in the clearly schizophrenic group. The psychosis with drug use cleared rapidly with hospitalization and antipsychotic drug treatment and relapsed only when drug use was resumed (164). If there is a true cannabis psychosis, this description is probably most accurate.

It would seem reasonable to assume that cannabis might unmask latent psychiatric disorders and that this action probably accounts for the great variety that have been described following its use. On the other hand, evidence for a specific type of psychosis associated with its use is still elusive. Hallucinogenic drugs have a similar property of unmasking latent illness, but a drug such as LSD, being much more disruptive to mental functioning than cannabis, is much more likely to precipitate a true psychosis or depression. Needless to say, use of cannabis should be discouraged (as would probably be the case with most socially used psychoactive drugs) in any patient with a history of prior emotional disorder (5).

5. Flashbacks. This curious phenomenon, in which events associated with drug use are suddenly thrust into consciousness in the nondrugged state, has never been satisfactorily explained. It is most common with LSD and other similar hallucinogens but has been reported fairly often with cannabis use. At first, it was thought that the phenomenon occurred only in subjects who had used LSD as well as cannabis, but more recent experience indicates that it occurs in those whose sole drug use is cannabis (153). One possibility is that flashbacks represent a kind of *deja vu* phenomenon. Another is that they are associated with recurrent paroxysmal seizurelike activity in the brain. The most unlikely possibility is that they are related to a persistent drug effect. They may occur many months removed from the last use of either LSD or cannabis, so that it is highly unlikely that any active drug could still be present in the body. Further, the interval between last drug use and the flashback is one in which the subject is perfectly lucid. For the most part, the reactions are mild and require no specific treatment.

6. Violence. The myth dies hard that cannabis makes otherwise docile subjects violent. Virtually every experimental study of cannabis that has tried to measure violent or aggressive behavior or thoughts during cannabis intoxication has come

to the same conclusion; they are decreased rather than increased. A study of 40 college students focussed specifically on this problem, comparing cannabis with alcohol. Expression of physical aggression was related to the quantity of alcohol taken, but not to any dose of THC (64). Similar findings have resulted from surveys (162). Aggressive and sexually assaultive behavior in delinquent adolescents was more common following use of alcohol, even in those who also used cannabis (168). A review of the whole subject of cannabis and violence came to the consensus that cannabis does not precipitate violence in the vast majority of users. The possibility was entertained that a rare individual with some special predisposition to aggressive or violent behavior may be triggered into expressing such behavior under the influence of the drug (2).

7. Amotivational syndrome. Whether chronic use of cannabis changes basic the personality of the user so that he or she becomes less impelled to work and to strive for success has been a vexing question. As with other questions concerning cannabis use, it is difficult to separate consequences from possible causes of drug use. It has long been postulated that the apparent loss of motivation seen in some cannabis users is really a manifestation of a concurrent depression, for which cannabis may have been a selfprescribed treatment (102).

The demonstration of such a syndrome in field studies has generally been unsuccessful. Cannabis use among working men in Costa Rica did not impair to any detectable degree their ability to function (26). Much the same was found among Jamaican laborers. No signs of apathy, ineffectiveness, nonproductiveness, or deficits in general motivation were found (38). Each of these approaches has been criticized on the basis that those surveyed were unskilled workers in whom subtle impairment might be difficult to detect. However, a study of college students came to similar conclusions (117). Little evidence was adduced that dropping out of college was associated with cannabis use. Family background, relationship with parents during high school, and social values were stronger forces than drug use. Thus, in subjects with moderate use patterns of cannabis, no evidence of the amotivational syndrome was detected (18). A similar survey of college students found no significant relationship between marijuana use and achievement, orientation, or actual performance (123).

Laboratory studies have provided only scant evidence for this concept. A Cana-

dian study showed a decrease in productivity following the smoking of cannabis. The decreased building of stools was due to less time worked than lessened efficiency at work (122). Using an operant paradigm, volunteer subjects on a research ward worked less as their consumption of cannabis increased. The decreased work output might have been due to decreased ability to work rather than decreased motivation (119). The former possibility is not suggested by neuropsychological testing of longterm users. No generalized decrement was observed in adaptive abilities or cerebral functions (24). Similar results were found in members of a United States religious sect that relies on cannabis use. They showed no impairment of cognitive functions on a number of neuropsychological tests (150).

If this syndrome is so difficult to prove, why does concern about it persist? Mainly because of clinical observations. One cannot help being impressed by the fact that many promising youngsters change their goals in life drastically after entering the illicit drug culture, usually by way of cannabis. While it is clearly impossible to be certain that these changes were caused by the drug (one might equally argue that the use of drug followed the decision to change life style). The consequences are often sad. With cannabis as with most other pleasures, moderation is the key word. Moderate use of the drug does not seem to be associated with this outcome, but when drug use becomes a preoccupation, trouble may be in the offing.

8. Residual psychomotor impairment. Almost any task, if it is made difficult enough or if enough dose of drug is given, can be shown to be impaired by acute administration of cannabis. More to the point is whether following chronic use impairment remains a problem. Experimental studies in rats suggest that it does, but such studies are always difficult to extrapolate to man (47). A comparison of 23 chronic users of bhang (equivalent to about 50 mg of THC daily for at least 5 years) with 11 nonusers revealed some evidence of impairment in the users. The latter had lower intelligence and memory quotients with lower scores on psychomotor tests (179). For whatever reasons, studies of cannabis done in India tend to show more evidence of impairment than those done elsewhere.

9. Brain damage. The startling report of cerebral atrophy in ten young men who were chronic users of cannabis aroused a great deal of controversy (22). The subjects selected for the study were ones who had come to psychiatric and neuro-

logical attention, besides which they had used other drugs. Even the validity of the method of measuring atrophy by comparing pneumocephalograms of the patients with negative controls was questioned. A study in monkeys provided some support for this observation. After 2 to 3 months of heavy to moderate exposure to marijuana smoke, electrographic recording changes were noted in the septal region, hippocampus, and amygdala which persisted 1 to 8 months after smoke exposure stopped. Ultrastructure changes were seen in synapses, as well as destruction of rough endoplasmic reticulum and the presence of nuclear inclusion bodies. No such changes were observed in animals exposed to smoke from extracted cannabis (73).

The advent of computerized tomography reopened the question. Two studies using this technique have effectively refuted the original claim of brain atrophy. Nineteen men with long histories of heavy cannabis smoking were examined, and none was found to have brain atrophy as determined by this sensitive technique (101). A similar finding was noted in the other study (33). On the other hand, alcohol has long been thought to cause brain atrophy, but recent studies suggest that it may be partially reversible (23). As brain atrophy from alcohol requires a substantial amount of use, it is possible that with longer exposure, heavy users of cannabis might show a similar pattern, but at present this seems unlikely.

F. Tolerance and Dependence

Tolerance to cannabis has long been suspected to occur during its continued use. Narrative accounts indicate that chronic users of the drug either show very little effect from moderate doses or require very large doses to produce characteristic intoxication. A pioneer study of subchronic administration of cannabis and synhexyl, a synthetic cannabinoid, suggests at best some degree of tolerance to the euphoriant actions (180). Yet it has only been in the past few years that tolerance to cannabis has been clearly documented experimentally.

The demonstration of tolerance in man was delayed by ethical restrictions on the amount of exposure permissible to human subjects. For instance, in an early study subjects were exposed only to a test dose of 20 mg of THC p.o. and then given the same doses or placebos repeated at bedtime for 4 more days, followed by the same THC dose as a challenge on the fifth day. Using such small doses and

relatively infrequent intervals, it was impossible to show tolerance to the psychic effects of the drug, although the tolerance to the tachycardia and dizziness produced by the drug were evident (85).

Other early studies likewise suggested tolerance without definite proof. Tolerance to both tachycardia and "high" was reported following 21 days of consecutive smoking of only one cigarette a day by experienced smokers. It was possible that these subjects may have already been tolerant to the drug (46). Another study, in which subjects smoked a cannabis cigarette containing 14 mg THC for 22 days, revealed a progressive decline in the increase of pulse rate following smoking, an increase in alpha rhythm on the electroencephalogram, and more decrement in the performance of shortterm memory and reaction time tasks (49).

A number of other early studies provided less evidence of tolerance. Little evidence of tolerance to clinical effects of cannabis was found from daily smoking of marijuana cigarettes over a period of 10 to 28 days (51, 142). Free choice of marijuana cigarette for 21 days also provided little evidence to support the concept of tolerance in man (165). Meanwhile, substantial evidence had accumulated that tolerance could be shown in various animal species, especially with high doses of THC given for prolonged periods.

Definite evidence of tolerance to the effects of THC in man was adduced only when it became permissible to use comparably large doses over longer periods of time. Subjects in one 30day study were given high doses (70 to 210 mg/day) of THC p.o. around the clock. Tachycardia actually became bradycardia, and a progressive loss of "high" was noted (49). Similar tolerance to cannabis smoking was observed in a 64day study in which at least one cigarette daily had to be smoked with smoking as desired later in the same day. Additionally, in this study tolerance developed to the respiratory depressant effect of THC (13).

The pattern that has emerged in man, therefore, is that tolerance is not a problem when the doses are small, or infrequent, or where the pattern of use of the drug is not prolonged. Tolerance only becomes a major factor with high, sustained, and prolonged use of the drug. It is interesting that no study in man or animals ever revealed any evidence for "reverse tolerance" or sensitization, such as had been reported in an early, rather naive clinical study of marijuana (176).

1. Crosstolerance. THC has effects which in man somewhat resemble those of hallucinogens and strongly resemble those of alcohol, while in animals it slightly resembles morphine. No crosstolerance to mescaline or lysergide (LSD) could be shown in rats (151). Rats tolerant to the effects of THC were also tolerant to ethyl alcohol, but when the situation was reversed, less tolerance to THC was seen in the alcohol-tolerant animals (127). Perhaps this difference in sequential tolerance is why THC has never become established as a treatment for alcohol withdrawal, despite some early clinical trials that suggested a favorable effect. Crosstolerance between THC and morphine has been shown in rats using customary tests of analgesia (95).

2. Physical dependence. Evidence from both animals and man indicates that physical dependence can be induced by abuse of THC. All monkeys given automatic injection doses of THC of 0.1 to 0.4 mg/kg showed abstinence signs when withdrawn. when monkeys were allowed to selfadminister the drug for 3 to 8 weeks, the majority had an abstinence syndrome when the drug was abruptly discontinued. the syndrome appeared approximately 12 h after the last administration and lasted about 5 days. it was characterized by irritability, aggressivity, tremors, yawning, photophobia, piloerection, and penile erections (95).

In man, a somewhat similar, though mild, withdrawal reaction was uncovered after abrupt cessation of doses of 30 mg of THC given every 4 p.o. for 10 to 20 days. Subjects became irritable, had sleep disturbances, and had decreased appetite. Nausea, vomiting, and occasionally diarrhea were encountered. Sweating, salivation, and tremors were autonomic signs of abstinence (49). Relatively few reports of spontaneous withdrawal reactions from suddenly stopping cannabis use have appeared, despite the extraordinary amount of the drug consumed, Five young persons experienced restlessness, abdominal cramps, nausea, sweating, increased pulse rate, and muscle aches when their supplies of cannabis were cut off. Symptoms persisted for 1 to 3 days (15). The rarity of reports of these reactions may reflect the fact that they are mild, and seldom is a user completely cut off from additional drug.

Cannabis would have been an exceptional centrally acting drug if tolerance/dependence were not one of its properties. The fact that tolerance was not strongly recognized as an effect of chronic use was due to the narrative nature of previous accounts of tolerance in man and the lack of systematic animal experimentation.

Tolerance has now been proven for most of the actions of THC. It develops at varying rates for different actions, but it is rapidly reversible. Large doses of THC are required over long time periods for tolerance to develop. As most social use of the drug does not meet those requirements, neither tolerance nor dependence has been a major issue in its social use.

G. Endocrine and Metabolic Effects

Changes in male sex hormones have been a source of controversy ever since the first report of a cannabinoid-induced decrease in serum testosterone level. Decreased levels were associated with morphological abnormalities in sperm and with decreased sexual functioning (100). Such changes must require long-term exposure to cannabis, for subchronic studies in experimental subjects have generally failed to confirm these findings (118). During the first 4 weeks of a chronic administration study, no major changes in hormone levels were detected, but with subsequent exposure a decrease first occurred in luteinizing hormone (LH) followed by decreases in testosterone and follicle-stimulating hormone (FSH) (99). Testosterone synthesis by Leydig cells was decreased in rats, both by THC as well as by other cannabinoids (21). A similar finding had been reported earlier (57). A review of the literature on this subject concluded that no significant effect was found in regard to serum testosterone and that sperm production was decreased but without evidence of infertility. Ovulation was inhibited, and luteinizing hormone was decreased. Cannabinoids had no evidence of estrogenic activity, which had been postulated earlier (4).

The meaning of such changes in man is uncertain, as the hormone levels generally remained within the accepted limits of normal. Further, a single hormone level may not be truly representative of the prevailing levels of hormones that tend to be secreted episodically or which are subject to many extraneous influences.

Data on the effects of cannabis on the female reproductive system are sparse. Preliminary unpublished data indicate that women who use cannabis 4 times a week or more have more anovulatory menstrual cycles than do nonusers of the same age. Animal work tends to support this observation. THC administered to rats suppressed the cyclic surge of LH secretion and of ovulation (11).

Gynecomastia has been thought to be a complication of cannabis use, especially when it was also possible to stimulate breast tissue development in rats with THC (72). Eleven soldiers with gynecomastia of unknown cause were matched with 11 others with similar characteristics except for gynecomastia. No difference in cannabis use was found between the two groups (27). Such a finding does not disprove the relationship between cannabis and gynecomastia. Indeed, if cannabis increases peripheral conversion of testosterone to estrogens, then it is possible that the increased estrogens could stimulate breast tissue in a few susceptible men. Increased estrogens might also account for some reports of diminution in sexual drive or in performance in men.

These endocrine changes may be of relatively little consequence in adults, but they could be of major importance in the prepubertal male who may use cannabis. At least one instance of pubertal arrest has been documented. A 16-year-old boy who had smoked marijuana since age 11 had short stature, no pubic hair, small testes and penis and low serum testosterone. After stopping smoking, growth resumed and serum testosterone reached the normal range (41). As recent surveys of cannabis use indicate that some boys (and girls) may be exposed to it even as early as the prepubertal years, this question is of more than academic interest.

Although cannabis has been said in the past to cause hypoglycemia, this error has been pointed out in numerous studies. On the contrary, some subjects showed impaired glucose tolerance following experimentally administered i.v. doses of 6 mg of THC. Such a dose is probably greater than one generally attains from usual cigarettes but might be obtained from high-grade hashish. The deterioration of glucose tolerance was accomplished by increased levels of plasma growth hormone, as well as by a normal plasma insulin response. These findings suggested that growth hormone might be interfering with the action of insulin (83). A study in rabbits indicated that blood glucose was increased by single doses of THC but that this increase could be prevented by adrenalectomy. Increased release of epinephrine following THC was postulated as a possible cause for the hyperglycemia (70). Although large doses of THC might aggravate diabetes, the rarity of this phenomenon in clinical practice may be due to the lower doses of THC used socially or the development of tolerance to this specific pharmacological effect.

H. Lung Problems

Virtually all users of cannabis in North America take the drug by smoking. As inhaling any foreign material into the lung may have adverse consequences, as is well proven in the case of tobacco, this mode of administration of cannabis might also be suspect. Smoking is most efficient method for administering the drug, due to the enormously high lipid solubility of THC. The pulmonary surfactant is a perfect trap for THC which is then rapidly absorbed into the blood. The kinetics of the THC administered by smoking are similar to those of its i.v. administration.

Heavy use of hashish by soldiers produced a number of bronchopulmonary consequences, including chronic bronchitis, chronic cough, and mucosal changes of squamous metaplasia, a precancerous change (74). Although at first THC was thought to be a respiratory depressant, more careful studies indicated that it was when given p.o. in doses of 22.5 mg (14). Thus, its use in any form by patients with impaired pulmonary function would be hazardous. Young, healthy volunteer subjects in a chronic smoking experiment had pulmonary function tests before and after 47 to 59 days of daily smoking of approximately five marijuana cigarettes a day. Decreases were found in forced expiratory volume in 1 s, in maximal midexpiratory flow rate, in plethysmographic specific airway conductance, and in diffusing capacity. Thus, very heavy marijuana smoking for 6 to 8 weeks caused mild but significant airway obstruction (161).

Quite possibly such dramatic early changes are not progressive with continued smoking (171). Compared with tobacco, cannabis smoking yields more residue ("tar"), but the amount of smoke inhaled is very likely to be considerably less. The study in which five cigarettes were consumed daily represented heavy use of the drug, compared with 20 to 40 tobacco cigarettes which might be consumed by a heavy tobacco smoker. Low values for specific airway conductance were found in marijuana smokers, a change not observed in tobacco smokers. This change indicates mild impairment of large airway function. No differences were found between marijuana smokers and nonsmokers in spirometric indices, closing volumes, or nitrogen concentrations between 750 and 1250 ml of expired air (159). Marijuana smoke inhibits pulmonary antibacterial defense systems, mainly alveolar macrophages, in a dose-dependent manner. The cytotoxin involved is not related to any psychoactive component (86). One would assume that marijuana

smokers might be more susceptible to bacterial infections of the lung, yet such increased susceptibility has not been clinically documented.

The issue of damage to lungs from cannabis is somewhat confounded by the fact that many cannabis users also use tobacco. As yet, it is far easier to find pulmonary cripples from the abuse of tobacco than it is to find any evidence of clinically important pulmonary insufficiency from smoking of cannabis.

I. Cardiovascular Problems

Tachycardia, orthostatic hypotension, and increased blood concentrations of carboxyhemoglobin from cannabis smoking would undoubtedly have deleterious effects on persons with heart disease due to arteriosclerosis of the coronary arteries or congestive heart failure. Although a slight trend toward increased use by persons over age 30 years has been detected in recent epidemiological studies, it is unlikely that many persons with serious heart disease will be exposed to this hazard from cannabis use.

Tachycardia is a consequence of almost every acute dose of cannabis, although some degree of tolerance develops to this effect. Evidence suggests that it is mainly due to an inhibition of vagal tone (32). Increasing the heart rate and thereby cardiac work might be harmful to patients with angina pectoris or congestive heart failure. A direct test of the effects of marijuana smoking in exercise-induced angina proved this harmful effect of the drug. Smoking one cigarette containing 19 mg of THC

decreased the exercise time until angina by 48%. Smoking a marijuana placebo cigarette decreased the exercise time until angina by only 9%. Thus, smoking marijuana increased myocardial oxygen demand and decreased myocardial oxygen delivery (9). A subsequent study compared the effect of this type of marijuana cigarette with that of a high nicotine cigarette. The marijuana cigarette decreased the exercise time by 50%; the nicotine cigarette decreased the exercise time to angina by 23% (10). Clearly, smoking of any kind is bad for patients with angina, but the greater effect of cannabis in increasing heart rate makes this drug especially bad for such patients. Fortunately, few angina patients are devotees of cannabis. A rapid heart rate might be expected to aggravate congestive heart failure. Actually,

little is known about the direct effects of THC on myocardium. A single study using an isolated rat heart reported a negative inotropic effect from THC, i.e., weaker contractibility of muscle (115). If so, the use of cannabis by patients in congestive heart failure could make matters even worse.

Premature ventricular contractions have been reported following marijuana smoking (91). However, when subjects were continually monitored electrocardiographically while smoking cigarettes containing approximately 20 mg of THC, no increase in such premature beats was found (145). Ventricular premature beats are rarely observed and do not seem to be of any great clinical importance.

J. Eye Problems

Eye complaints of cannabis users are vague and mild. All 350 cannabis users had some eye complaints. Several consistent findings were (a) photophobia and bellarospasms; (b) injection of the globe; (c) increased visibility of the corneal nerves; and (d) accommodative or refractive changes. Visual acuity was preserved, but pupillary reactions were sluggish. Both alcohol and cannabis produced a moderately debilitating effects on lateral phoria and abduction. During smoking, lacrimation may be observed along with the characteristic marked conjunctival injection. Despite the fact that numerous and complex changes occur in the eyes of cannabis users, these effects are confined to the anterior segment and in most respects mimic an irritative process of that region. they are transient and not cumulative. they are probably of little clinical significance (60).

Reduction intraocular pressure is a characteristic effect from cannabis. this action provides distinct therapeutic possibilities and will be discussed later.

K. Contamination of Cannabis

The most definite health hazard was contamination of cannabis, largely of Mexican origin, by the herbicide paraquat. Inhalation of toxic amounts of this material could lead to severe lung damage, and some instances of acute toxicity have occurred. Paradoxically, this hazard stemmed from efforts to save cannabis users from less well-documented hazards to their health.

Estimates of the amount of contaminated cannabis reaching North America may have been grossly exaggerated due to false positive results in testing for paraquat. Formerly as much as one-third to one-half of Mexican cannabis was assumed to be contaminated. the results of later analyses suggest that only about 10% is contaminated. the problem still remains for the users as to how to identify such a contaminated product.

One thought has been to look for red spots on the marijuana leaves. this approach may be difficult for the leaves are usually available in a finely ground form. A red fluorescence is seen under ultraviolet light, such as is commonly used in discotheques. A similar red fluorescence may be seen on the lips of the smoker of paraquat contaminated cannabis.

After the experience with paraquat in Mexico, its use was temporarily discontinued. Recently, the possibility that it may be used against cannabis crops in California and Hawaii has surfaced. One would hope that overzealous law enforcement would not once again pose a serious health risk to marijuana users.

Cannabis is generally harvested like any other crop. The final product of ground leaves and stems look very much like grass cut by a mower. usual insecticides and fungicides are rarely used, as the plant grows abundantly with minimal care. Other sources of contamination may include insects and fungi.

L. Possible Accumulation of Drug

The major if not sole active component of cannabis, THC, is highly lipid soluble. As the human body has a high lipid content, which includes not only body fat, but also brain and most cell membranes, lipidsoluble drugs tend to leave the blood rapidly to be distributed to fatty tissues. It is characteristic of such drugs that the action of a single dose is terminated not by the elimination of the drug through metabolic processes, but by redistribution to sites in the body where it cannot act. The prime example of such a drug is pentothal sodium, which rapidly produces anesthesia when given i.v. but which has a very short span of action. the drug still remains in the body, but in places where it cannot act. A similar situation applies to the widely used sedative drug, diazepam.

An early study of the pharmacokinetics of THC examined its tissue distribution following a single injection of radiolabeled material, the concentration of THC in fat was 10 times greater than for any other tissue examined and persisted in this tissue for 2 weeks. Thus, there is good evidence that THC and its metabolites might accumulate not only in fat, but also in brain (107).

Obviously, similar studies could not be done in man. One can measure in man the extraction of cannabis metabolites following single or repeated doses, to get some idea of their persistence. Following both single and repeated doses (at least single doses for several days), metabolites of cannabis can be found in urine for varying periods, up to several days following the last dose (94). All of these metabolites are ones that are known to have no mental effects, except for a minuscule amount of unchanged THC which is excreted during the first 4 h following a dose, while the drug is having definite clinical effects. The excretion of these metabolites is not accompanied by any evidence of cannabislike effects.

We may conjecture that THC rapidly leaves the blood to be sequestered in fatty tissues. It is either gradually metabolized in these tissues to inactive metabolites which are then excreted in the urine, or it may be gradually released from these tissues in small amounts to be metabolized by the liver before attaining effective plasma concentrations. In either case, there is no evidence of a continuing drug effect from this accumulation of drug in the body.

No one has yet reported on the excretion of metabolites following prolonged exceedingly high dose administration of THC. In one study in which doses of up to 210 mg of THC were given p.o., abrupt discontinuation of the drug led quickly to mild signs of a withdrawal reaction (49). As the development of withdrawal reactions is contingent upon a rapid decline to the point of absence of active drug in the body, one must assume that no accumulation of active drug occurred even under extreme circumstances.

In short, the apprehension about accumulation of THC from repeated use is based on evidence indicating only the accumulation of drug that is either in inactive form to begin with or which is rendered inactive before reaching the circulation in any pharmacologically active amount. We do not know the full toxicity of many of the possible metabolites which might accumulate, but generally toxicity studies

of cannabis and its constituents lead to the inescapable conclusion that it is one of the safest drugs ever studied this way.

M. Effects on Driving an Automobile

If marijuana is to become an accepted social drug, it would be important to know its effects on driving ability. Fully one-half of the fatal car crashes in the United States are associated with another social drug, alcohol. Neither experimental nor epidemiological approaches to the marijuana question have yet provided definitive answers.

Many studies have used acute doses of marijuana or THC to study various psychomotor functions. These can be summarized by saying that, if the dose of drug was high enough or the task difficult enough, impairments were shown. It is difficult to determine how pertinent these tests are to the actual driving of an automobile. Furthermore, it is difficult to relate the effects of acute consumption of marijuana, often in relatively naive subjects, to effects that may be found in chronic users, who may have developed some degree of tolerance.

Studies on the acute effects of marijuana on simulated driving have shown mixed results. The first compared smoked marijuana (doses uncertain) with ethanol in sufficient quantities to produce alcohol levels of 100 mg/dl. Marijuana increased speedometer errors but produced no deviation from the norm on accelerator, brake, signal, steering, or total errors. Alcohol had a far more deleterious effect (43). Marijuana administered p.o. in doses of 8, 12 and 16 mg was compared with a dose of 70 g of alcohol in eight volunteer subjects performing a simulated driving task. Both marijuana and alcohol increased the time to brake and to start, but these changes were confined to the 16 mg dose of THC (138). Marijuana was smoked with the intention of administering doses of 0, 50, 100, and 200 µg/kg, a most dubious assumption. No significant deviations from the norm were noted in car control and tracking aspects (124).

Actual driving in normal traffic situations would more closely mimic real-life situations, including the dangers. Sixty-four volunteer subjects smoked cigarettes containing 0, 4.9, or 8.4 mg of THC. Oddly enough, THC had a biphasic effect, causing deterioration of driving skills in some subjects and improvement in others. A

recently completed study compared the effects of smoking a marijuana cigarette with or without alcohol, alcohol alone, and placebos for each drug. Actual driving was done over a course rigged with various traffic problems. Both drugs produced impairment of driving performance, the combination being worse than either alone (141).

Fifty-nine subjects smoked marijuana cigarettes until "high" and then were periodically tested by highway patrol officers on the roadside sobriety test. Overall, 94% of the subjects failed to pass the test 90 min after smoking and 60% after 150 min, despite the fact that by then plasma concentrations of THC were rather low (81). It appeared that establishing a clear relation between THC plasma concentrations and the degree of clinical impairment will be much more difficult than has been found in the case of alcohol (140). The exact prevalence of persons who might be picked up while driving under the influence of marijuana is uncertain. One survey found at least 5 ng of THC per ml in blood specimens of 14.4% of a random sample of 1792 drivers detained for erratic driving. Many were associated with blood levels of alcohol as well (184). Flying an airplane is much more difficult than driving an automobile, but the general principle of impairment are similar. Ten certified pilots who smoked marijuana or placebo were tested on a simulator. The results were highly variable from pilot to pilot and from skill to skill.

It was assumed that the pilots had regained full function after 4 h (90). Somewhat contrary results were obtained in another similar study which found, however, some degree of impairment in flying skills as long as 24 h after an exposure to marijuana. The subjects were unaware of any such impairment (182).

The issue is not clearly settled, but common sense would suggest that it would be unwise to try to drive an automobile soon after exposure to marijuana. In our first study with the drug, the subjects were asked during the period of their intoxication, "Would you be able to drive a car now?" Their uniform answer was, "You've got to be kidding." The biggest areas of doubt are how long the impairment, even though subtle, may last and how to deal forensically with driving while under the influence of marijuana. The best evidence at present would be to assume that any amount of THC more than 10 ng/ml in plasma is presumptive evidence of impairment. Such a decision is arbitrary, but so have been forensic decisions about the presumed level of intoxication with alcohol.

IV. Therapeutic Uses

For many centuries, cannabis was used as a treatment, but only during the 19th century did a particularly lively interest develop for exploiting its therapeutic potential. Cannabis was reported to be effective in treating tetanus, convulsive disorders, neuralgia, migraine, dysmenorrhea, post partum psychoses, senile insomnia, depression, and gonorrhoea, as well as opium or chloral hydrate addiction. In addition, it was used to stimulate appetite and to allay the pain and anxiety of patients terminally ill with cancer (64, 121). However, the advent of modern pharmacology beginning in the 20th century discovered many other drugs more definitely effective in these disorders, with a subsequent decrease in the enthusiasm for cannabis as a therapeutic agent.

Advances in the chemistry of cannabis during the 1940s established tetrahydrocannabinol (THC) as the major active component. A semisynthetic THC-like material, synhexyl, was tested as a therapeutic agent during the late 1940s and early 1950s. Initial trials reported efficacy as an antidepressant and as a treatment for alcohol or opiate withdrawal, but subsequent clinical evaluations were negative (156,166).

The exact structure of THC was shown in 1964 to be delta-9-trans tetrahydrocannabinol, which was soon synthesized. The relative abundance of this material permitted extensive laboratory and clinical studies from 1968 onwards. These studies have included potential therapeutic uses.

At the present time, a number of pharmaceutical houses have programs to develop cannabinoids as therapeutic agents. The major problem is to separate the specific desired pharmacological effect from the pronounced mental effects of cannabinoids. A number of reviews of the potential therapeutic uses of cannabis have been published recently (36, 92, 104). We will now discuss some indications of current interest.

A. Antiemetic for Patients in Cancer Chemotherapy

Cancer chemotherapy, especially with the agent cisplatin, produces severe nausea and vomiting, which is extremely difficult to treat with ordinary antiemetic

drugs, such as prochlorperazine. This complication is so severe that many patients forego effective cancer chemotherapy. The antiemetic effects of cannabis had been suggested as early as 1972 (6). THC was first tried as an antiemetic in a controlled trial comparing it with placebo in 20 patients undergoing cancer chemotherapy. Fifteen mg were given to some patients and 20 mg to the others in the form of gelatin capsules containing THC dissolved in sesame oil. The initial dose was started 2 h before chemotherapy and repeated 2 and 6 h later. Fourteen of the 20 patients in whom an evaluation could be made reported a definite antiemetic effect from THC, while none was observed from placebo during 22 courses of that drug (149).

Since then, studies have been largely confirmatory but not entirely so. Fiftythree patients refractory to other treatments were studied in an uncontrolled fashion. Ten had complete control of vomiting when THC was administered prior to chemotherapy and for 24 h thereafter. Twentyeight had 50% or more reduction in vomiting, and only 15 patients showed no therapeutic effect whatsoever. However, four patients were dropped from the study because of adverse effects (113).

Fifteen doses of 15 mg of THC were compared with 10mg doses of prochlorperazine in a controlled crossover trial in 84 patients. THC produced complete response in 36 of 79 courses, while prochlorperazine was effective in only 16 of 76 courses. Twenty-five patients received both drugs, of whom 20 preferred THC. Of the 36 courses of THC that resulted in complete antiemetic response, 32 were associated with mental effects characterized as a "high" (148). Another comparison between THC in 15mg doses and prochlorperazine in 10mg doses versus a placebo control was made in 116 patients who received p.o. doses 3 times a day. The THC regimen was equal to prochlorperazine, and both were superior to placebo. However, many patients who received THC found it to be unpleasant (55).

A comparison of THC with placebo was made in 15 patients with each patient acting as his or her control. Fourteen of the 15 patients given THC obtained more relief of nausea and vomiting than from placebo during a course of highdose methotrexate chemotherapy (28). Best results were obtained when plasma concentrations of THC were more than 120 ng/ml. Such concentrations would ordinarily be expected to produce rather definite mental effects, THC was compared with two other antiemetics, thiethylperazine and metoclopramide, in a controlled cross-

over trial. No difference was found between the antiemetic effect of these three agents. However, adverse effects of THC were sufficiently greater than those from the other two drugs, which raised questions about its clinical utility (37). When THC was compared with prochlorperazine and placebo, the latter two treatments were not found to differ, but THC was superior to either one (131).

In summary, it would appear that THC has definite antiemetic effects, that these are comparable to many other commonly used antiemetic agents such as prochlorperazine, thiethylperazine, and metoclopramide, but that the major disadvantage of the drug is the mental effects produced by the doses given.

A synthetic homolog of THC, nabilone, was developed in 1972 and has been tested extensively for antiemetic activity. A crossover study comparing nabilone with prochlorperazine in 113 patients revealed significantly greater response rates following nabilone therapy. However, side effects from nabilone were also more common (77). Although it was hoped that nabilone separated the antiemetic effects from the mental effects of THC, this goal was not fully achieved. Levonantradol and BRL 4664 are two other synthetic THC homologs which showed antiemetic effects in open studies (43, 154). The exact role of synthetic homologs of THC as antiemetic agents remains to be determined.

Currently, a large amount of data on the clinical use of THC as an antiemetic is being accumulated in therapeutic situations monitored by the Food and Drug Administration. Unfortunately, this massive amount of clinical experience has no control, so that it may be impossible to conclude more than what is already known. Meanwhile, extremely promising results have been obtained with larger than usual i.v. doses of metoclopramide. When this drug was compared with prochlorperazine and placebo, it was more effective than either, the only disturbing side effect being sedation (59). The doses used of metoclopramide were 1 mg/kg i.v. before treatment with cisplatin (perhaps the most emetic anticancer drug) and several times after treatment. Protection was total in 48% of courses and major in another 23% (157).

This experience with metoclopramide suggests that the whole issue of the antiemetic effects of THC may become moot, as there are other drugs such as domperidone, which may also be effective in this situation.

B. Glaucoma

Discovery of the ability of cannabis to lower intraocular pressure was more or less fortuitous. Intraocular pressure was measured as part of a multifaceted study of the effects of chronic smoking of large amounts of cannabis. Intraocular pressure was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking (75). Lowered intraocular pressure lasted 4 to 5 h after smoking a single cigarette. Its magnitude was unrelated to the total number of cigarettes smoked. The maximal effect on intraocular pressure was produced by the amount of THC absorbed in a single cigarette containing 19 mg of THC. When patients with ocular hypertension or glaucoma were tested 7 of 11 showed a fall of intraocular pressure of 30%. Confirmatory evidence was obtained from a trial in which i.v. injection of THC in doses of 22 $\mu\text{g}/\text{kg}$ and 44 $\mu\text{g}/\text{kg}$ produced an average fall in intraocular pressure of 37%, with some decreases as much as 51% (40).

Many experiments done in rabbits using various routes of administration, including instillation of cannabinoids into the eye, have confirmed the ability of cannabis to reduce intraocular pressure.

Topical administration would be especially desirable for treating glaucoma as with other drugs used for this purpose. Smoking cannabis or taking THC i.v. would be totally unsuitable for patients with glaucoma. Rabbits have been used traditionally for studying eye medications. The lipid solubility of THC has been overcome by using mineral oil as the vehicle for its instillation into the eye. The degree of lowering of intraocular pressure is at least as great as that with conventional eye drops, such as pilocarpine, and the duration of effect is often longer. Some minimal systemic absorption of the drug occurs when it is applied to the conjunctivae, but it is of no consequence in producing mental effects. Other cannabinoids besides THC, such as cannabinal or 8α and 8β - 11 -dihydroxy- Δ^9 -THC, have also produced this effect in rabbits (62). These agents have no mental effects, which makes them of considerable interest for therapeutic use.

An extract of nonpsychoactive components of cannabis whose composition is still uncertain has been tested both alone and in combination with timolol eye drops in patients with increased intraocular pressure. The effects of the two agents are additive and are said to be effective when other measures have failed (177). BW

146Y, a synthetic THC homolog, has been given p.o. to glaucomatous patients. Unfortunately, mild orthostatic hypotension and subjective effects were noted in addition to reduced intraocular pressure (167).

No psychoactive component of cannabis can be considered as a feasible therapeutic agent in this situation. Intraocular pressures, although they are reduced acutely, have not been shown to be reduced following longterm treatment, nor has there been any demonstration that visual function is preserved by the use of cannabinoids in glaucoma. Some of the problems associated with the development of cannabinoids as treatment for glaucoma have already been cited (61). The exploitation of cannabinoids for treatment of glaucoma will require much further developmental work to ascertain which cannabinoid will be lastingly effective and well tolerated. The potential benefits could be great, as presentday glaucoma treatment still does not prevent blindness as often as it might. If the effects of cannabinoids are additive to those of other drugs, the overall benefit to patients may be greater than is currently possible with single drugs.

C. Analgesia

Smoking of material estimated to deliver 12 mg of THC increased sensitivity to an electric shock applied to the skin (78). Single p.o. doses of 10 mg and 20 mg of THC were compared with codeine (60 mg and 120 mg) in patients with cancer pain. A 20 mg dose of THC was comparable to both doses of codeine. The 10 mg dose, which was better tolerated, was less effective than either dose of codeine (129). THC given i.v. in doses of 44 $\mu\text{g}/\text{kg}$ to patients undergoing dental extraction produced an analgesic effect, which was less than that achieved from doses of 157 μg of diazepam per kg i.v. Several of these patients actually preferred placebo to the dose of 22 μg of THC per kg because of anxiety and dysphoria from the latter drug (139).

The apparent paradox is that THC both increases and decreases pain. Traditionally, aspirinlike drugs, which work peripherally by inhibiting the synthesis of prostaglandins, are used to treat pain derived from the integument. The initial mental stimulation from THC might increase sensitivity to this kind of pain. Visceral pain, such as that of cancer patients, is usually treated by opiates, which have both peripheral and central sites of action. Recent evidence suggests that opiates may

act directly on pain pathways in the spinal cord as well as reducing the effect that produces pain. Cannabis could conceivably modify the effective response. Thus, when the two types of pain are distinguished from each other, the apparent paradox is solved.

THC, nantadol, and nabilone shared some properties with morphine in chronic spinal dog model. Latency of the skin twitch reflex was increased, and withdrawal abstinence was suppressed. Naltrexone did not antagonize these actions, suggesting that they are not mediated through opiate receptors (56). Levonantradol i.m. was compared with placebo in postoperative pain, and a significant analgesic action was confirmed. No doseresponse relationship was observed, and the number of side effects from levonantradol was rather high (89). It seems unlikely that any THC homolog will prove to be analgesic of choice, when one considers the present array of very effective new analgesics of the agonistantagonist type. It is too early to be sure, however.

D. Muscle Relaxant

Patients with spinal cord injuries often selftreat their muscle spasticity by smoking cannabis. cannabis seems to help relieve the involuntary muscle spasms that can be so painful and disabling in this condition. A muscle relaxant or antispastic action of THC was confirmed by an experiment in which p.o. doses of 5 or 10 mg of THC were compared with placebo in patients with multiple sclerosis. The 10 mg dose of THC reduced spasticity by clinical measurement (135). Such single small studies can only point to the need for more study of this potential use of THC or possibly some of its homologs. Diazepam, cyclobenzaprine, baclofen, and dantrolene, which are used as muscle relaxants, all have major limitations. A new skeletal muscle relaxant would be most welcome.

E. Anticonvulsant

One of the first therapeutic uses suggested for cannabis was as an anticonvulsant. Such an effect was documented experimentally many years ago (112). Subsequent studies in various animal species have validated this action. THC in cats temporarily reduced the clinical and electrographic seizure activity induced by electrical stimulation of subcortical structures (175). Mice were protected by can-

nabidiol against maximal electroshock seizures but not against those caused by pentylenetetrazole. Its profile of activity more resembled that of phenytoin than that of THC (170). THC and cannabidiol both potentiated the anticonvulsant effects of phenytoin against electrically induced seizures in mice. The two cannabinoids in combination produced the most effect (29). Kindling involves the once-daily application of initially subconvulsive electrical stimulation to culminate in generalized convulsive seizures. THC given chronically to rats prevented the kindling effect (174).

Clinical testing has been rare, despite all these various lines of evidence supporting an anticonvulsant effect of cannabinoids. Better control of seizures following regular marijuana smoking was reported in a not very convincing single case (39). Fifteen patients not adequately controlled by anticonvulsants were treated with additional cannabidiol in doses of 200 or 300 mg or placebo. Cannabidiol controlled seizures somewhat better than the addition of placebo (25). Cannabidiol has little if any psychoactivity, making it a good candidate for this use.

F. Bronchial Asthma

A general study of the effects of marijuana on respiration revealed a bronchodilating action in normal volunteer subjects. Marijuana smoke was calculated to deliver 85 or 32 μg of THC per kg. A fall of 38% in airway resistance and an increase of 44% in airway conductance occurred in the highdose group. The lowdose group showed lesser changes, but they were still significant as compared with baseline. The sensitivity of the respiratory center to carbon dioxide was not altered by either dose, indicating no central respiratory depression (172).

Asthma was deliberately induced by either inhalation of methacholine or exercise in asthmatic patients. They were then treated with inhalation of placebo marijuana, of saline, of isoproterenol, or of smoke derived from marijuana containing 1 g of THC. Both marijuana smoke and isoproterenol aerosol effectively reversed both methacholine- and exerciseinduced asthma, while saline and placebo marijuana had no effect (160). Aerosols of placeboethanol, of THC (200 μg) in ethanol, or of salbutamol (100 μg) were tested in another study of ten stable asthmatic patients. Forced expiratory volume in 1s forced vital capacity, and peak flow rate were measured on each occasion. Both salbutamol and THC significantly improved ventila-

tory function. Improvement was more rapid with salbutamol, but the two treatments were equally effective at the end of 1 h (181).

Both delta8 and delta9THC have bronchodilating effects, while neither cannabinol nor cannabidiol has such actions. Thus, this action resides only in the psychoactive material. No evidence of tolerance to this effect developed over 20 days of continual administration (58). The treatment of asthma is much more chronic; further studies of tolerance will be needed.

Some patients might experience bronchoconstriction following THC. Doses of 10 mg p.o. produced mild and inconsistent bronchodilator effects as well as significant nervous system effects. One patient of the six studied developed severe bronchial constriction (1). Mild but significant functional impairment, predominantly involving the large airways, was found in 74 regular smokers of cannabis. Such impairment was not detectable in individuals of the same age who regularly smoked tobacco (64).

THC would be best administered by aerosol for this purpose, but whether effective doses would avoid the mental effects is uncertain. The mechanism of action by which THC increases airway conductance may be different from the usual betaadrenergic stimulants. Resistance to repeated applications of betaadrenergic stimulants does occur. Another type of bronchodilator might help some patients. The recent introduction of highly effective steroid aerosols, such as beclomethasone, meets that need to a considerable extent.

G. Insomnia

THC does not differ from conventional hypnotics in reducing rapid eye movement (REM) sleep (136). THC in doses ranging from 61 to 258 µg/kg produces in normal subjects increments in stage 4 sleep and decrements in REM sleep, but without the characteristic REM rebound which follows chronic treatment with hypnotics. When THC was administered p.o. as a solution in doses of 10, 20, and 30 mg, our subjects fell asleep faster after having mood alterations consistent with a "high." Some degree of "hangover" the day following was noted from larger doses (42). Another sleep laboratory study showed that a dose of 20 mg of THC given p.o. decreased REM sleep. After four to six nights of use, abrupt discontinuation of THC

produced mild insomnia but not marked REM rebound (52). REM rebound may not be apparent after low doses of THC. However, very high doses (70 to 210 mg) reduced REM sleep during treatment and were followed by marked REM rebound after withdrawal (48).

The sleep produced by THC does not seem to differ much from that of most currently used hypnotics. Side effects before sleep induction as well as hangover effects make the drug less acceptable than currently popular benzodiazepines. It seems unlikely that THC will supplant existing hypnotics in treatment of insomnia.

H. Miscellaneous Uses

1. Hypertension. Orthostatic hypotension occasionally follows use of THC (5). A dimethylheptyl sidechain derivative has more profound and constant effects on blood pressure. In man, this compound showed a marked orthostatic hypotensive effect, as well as tachycardia and some mental symptoms resembling THC. While the latter are less than from THC in proportion to the blood pressurelowering effect, a definite separation of pharmacological effects has not been attained (106).

Effective antihypertensive drugs have been one of the outstanding achievements of pharmacology over the past 30 years. A new antihypertensive based on orthostatic hypotension, perhaps the least desirable mode of lowering blood pressure, is hardly very enticing (8). The issue seems hardly worth pursuing further.

2. Abstinence syndromes due to central nervous system depressants.

Synhexyl, the first THC homolog to be synthesized, was tested as a treatment for withdrawal reactions from opiates and alcohol with little evidence of efficacy. Withdrawal symptoms experienced by rats following morphine pellet implantation, followed by subsequent injection of naloxone, were reduced by THC. Cannabidiol, without any direct effect itself, augmented the action of THC (79).

3. Antineoplastic activity

Both the delta8 and delta9THC isomers, as well as cannabinol, have some antineoplastic effect on transplanted lung tumors in animals, as well as on tumors

in vitro (125). THC may have a general ability to reduce the synthesis of nucleic acids, which may account for reported immunosuppressant effects as well. Many agents are available that inhibit nucleic acid synthesis, so the possibility that THC or other cannabinoids might be advantageous seems rather unlikely.

4. Antimicrobial action

Both THC and cannabidiol inhibit and kill staphylococci and streptococci in vitro at concentrations of 1 to 5 µg/ml (173). Such concentrations are well above those reported for use of THC in man, even at the highest tolerated doses. Thus, this effect seems to have little practical application.

5. Migraine

This indication has not been studied systematically in recent years, although it has a long history. In one patient I treated, the mental effects sought socially caused the patient to abandon treatment. Innumerable successful treatments for migraine have been reported at one time or another.

6. Appetite stimulant

Most antipsychotic agents will stimulate appetite, but few other drugs do. THC as compared with ethanol and dextroamphetamine produced a variable response on appetite, both in fed and fasted subjects. The majority had increased appetite and food consumption as compared with placebo (80). Anorexia nervosa might be helped by an appetite stimulant. A test of the presumed appetitestimulating properties of THC in patients with anorexia nervosa failed over a 4week period. Doses of THC ranged between 7.5 and 30 mg/day and were compared with 30 mg of diazepam per day and placebo. Three of the 11 patients treated with THC experienced severe dysphoria (65).

7. Alcoholism

Cannabis users are said not to drink, but most do. The prospect of changing an alcoholic into a cannabinolic has some appeal. A study showed that cannabis was not very attractive to alcoholics. Little difference in retention occurred among

those given no medication, or a cannabis cigarette, or disulfiram or the combination of the cigarette and disulfiram (143).

V. Summary

Marijuana seems firmly established as another social drug in Western countries, regardless of its current legal status. Patterns of use vary widely. As with other social drugs, the pattern of use is critical in determining adverse effects on health. Perhaps the major area of concern about marijuana is among the very young. Using any drug on a regular basis that alters reality may be detrimental to the psychosocial maturation of young persons. Chronic use of marijuana may stunt the emotional growth of youngsters. Evidence for an amotivational syndrome is largely based on clinical reports; whether marijuana use is a cause or effect is uncertain. A marijuana psychosis, long rumored, has been difficult to prove. No one doubts that marijuana use may aggravate existing emotional disorders. Brain damage has not been proved. Physical dependence is rarely encountered in the usual patterns of social use, despite some degree of tolerance that may develop. The endocrine effects of the drug might be expected to delay puberty in prepubertal boys, but actual instances have been rare. As with any material that is smoked, chronic smoking of marijuana will produce bronchitis; emphysema or lung cancer have not yet been documented. Cardiovascular effects of the drug are harmful to those with preexisting heart disease; fortunately the number of users with such conditions is minimal. Fears that the drug might accumulate in the body to the point of toxicity have been groundless. The potential deleterious effects of marijuana use on driving ability seem to be selfevident; proof of such impairment has been more difficult. The drug is probably harmful when taken during pregnancy, but the risk is uncertain. One would be prudent to avoid marijuana during pregnancy, just as one would do with most other drugs not essential to life or wellbeing. No clinical consequences have been noted from the effects of the drug on immune response, chromosomes, or cell metabolites. Contamination of marijuana by spraying with defoliant has created the clearest danger to health; such attempts to control production should be abandoned.

Therapeutic uses for marijuana, THC, or cannabinoid homologs are being actively explored. Only the synthetic homolog, nabilone, has been approved for use to control nausea and vomiting associated with cancer chemotherapy. While little

doubt remains that marijuana, THC, and nabilone are effective for this use, the advent of other drugs that are equally effective but with fewer adverse effects may make this use moot. Use of marijuana to reduce intraocular pressure in patients with glaucoma requires a feasible topical preparation of cannabinoids. Although some cannabinoids have analgesic activity, the abundance of new opioid analgesics with little dependence liability provides tough competition. The use of marijuana as a muscle relaxant, though promising, has not yet been adequately studied. Clinical studies to establish the efficacy of cannabidiol as an anticonvulsant or to compare it with other anticonvulsants are still to be done. Other potential therapeutic uses, such as treatment of bronchitis, asthma, insomnia, hypertension, abstinence syndromes, migraine, anorexia, and alcoholism, are most unlikely prospects.

Compared with other licit social drugs, such as alcohol, tobacco, and caffeine, marijuana does not pose greater risks. One would wonder, however, if society were given a choice based on current knowledge, whether these drugs would have been granted their present status of acceptance. Marijuana may prove to have greater therapeutic potential than these other social drugs, but many questions still need to be answered.

The International Journal Of The Addictions • May 1985

Therapeutic issues of marijuana and THC (tetrahydrocannabinol)

Ungerleider JT, Andrysiak T.

<http://www.ncbi.nlm.nih.gov/pubmed/2995262>

This article summarizes current knowledge about the medicinal value of cannabis and its principal psychoactive ingredient, delta 9-tetrahydrocannabinol (THC), particularly in the control of nausea and vomiting, in glaucoma, and in reduction of spasticity in multiple sclerosis. The major issues in the controversy about marijuana and medicine, primarily moral and ethical, are discussed.

Acute, short-term, and chronic effects of marijuana on the female primate reproductive function

Smith CG, Asch RH.

<http://www.ncbi.nlm.nih.gov/pubmed/6090911>

Studies with laboratory animals clearly show that the crude drug marijuana and delta-9-THC, the principal psychoactive ingredient, inhibit secretion of the pituitary hormones LH and FSH as well as prolactin. These changes in pituitary hormone levels produce decreases in sex steroid hormones and cause disruption of ovulation and spermatogenesis. With chronic drug use, disruption of sex accessory organs has also been observed. A principal site of THC action is the hypothalamus, because THC effects on pituitary hormone production can be reversed with hypothalamic releasing factors. It is now known that drug effects in sexually mature animals are reversible when drug treatment stops. In adults, tolerance develops to hormone changes brought on by the use of marijuana. Clinical studies on human subjects generally agree with the animal findings, although conflicting results have been reported as well. It is likely that the differences in results obtained in experiments with laboratory animals and with humans are caused, at least in part, by differences in experimental design. Further, it is not known how much disruption of reproductive hormone levels is necessary for changes in human fertility and sexual function to occur. The use of marijuana by pregnant women or by women who are attempting to become pregnant is cause for special concern. Studies with laboratory animals and retrospective studies on women who have used marijuana during pregnancy show that the risks of pregnancy loss and other adverse effects on the fetus are increased by marijuana use. THC crosses the placental barrier and while the potent teratogenic and mutagenic effects suggested for marijuana some years ago have not been confirmed, significant changes consistent with retardation of fetal growth and development have been observed. Effects of THC on the proper functioning of the placenta may be responsible for these effects on pregnancy. Pregnancy that occurs after the development of tolerance with chronic marijuana use may involve an ovum that has been damaged by exposure to the drug during critical developmental stages. More studies need to be done before the mechanisms of toxic effects on pregnancy and fetal development can be described. While there have been no clinical studies relating marijuana use to adolescent development, studies in laboratory animals show that the developing reproductive system during adolescence is particularly vulnerable.

Endocrine effects of marijuana in the male: preclinical studies

By J. Harclerode

<http://www.ncbi.nlm.nih.gov/pubmed/6090909>

Marijuana affects a variety of hormones that are regulated by hypothalamic function and it appears that the psychoactive ingredient, THC, is the major compound responsible for this action. It is probable that THC affects these hormones through its ability to alter various neural transmitters in the hypothalamus or neural transmitters in the CNS which impinge on the hypothalamus. The dopaminergic and serotonergic fibers seem to be particularly important. The two gonadotropins, LH and FSH, secreted by the pituitary gland are of major importance to reproduction in the male. Both gonadotropins appear to respond to a single releasing factor from the hypothalamus, GnRH, which is sensitive to catecholamine neurotransmitters. The THC-induced block of GnRH release results in lowered LH and FSH which is responsible for reduced testosterone production by the Leydig cells of the testis. Other hormones that might have a synergistic or antagonistic effect upon reproduction in the male are the adrenal cortical hormones, prolactin, thyroid hormones, and growth hormones. THC appears to depress prolactin, thyroid gland function, and growth hormone while elevating adrenal cortical steroids. Chronic exposure of laboratory animals, such as rats, mice, and monkeys to marijuana and to the various cannabinoids in marijuana has altered the function of several of the accessory reproductive organs. Reports of reduced prostate and seminal vesicle weights, as well as altered testicular function, have been partially explained by the effect of marijuana in lowering serum testosterone needed for proper function and support. Although some of the change in organ weight may be due to lowered testosterone production by the Leydig cells of the testis, some of the weight changes may be due to a direct action of THC, and perhaps some of the other nonpsychoactive cannabinoids in marijuana, on the tissue themselves. Also, of concern are the reports that acute cannabinoid treatments affects the quality and quantity of spermatozoa produced by the testis. The question is still unanswered as to whether or not the effects observed on spermatozoa are due to a direct action of the cannabinoids on spermatogenesis, or whether some of the observed effects may be due to altered hormone levels which are necessary for the support of spermatogenesis. Reduced testosterone and FSH may be important in producing the observed changes in sperm production by the seminiferous tubules. Many of the effects on the endocrine system caused by chronic treatment of animals with THC are completely reversible with time and there is reason to believe that tolerance develops to these effects with acute exposure to THC.

Endocrine aspects of cannabinoid action in female subprimates: search for sites of action

By L. Tyrey

<http://www.ncbi.nlm.nih.gov/pubmed/6090910>

The search for a site of cannabinoid action in non-primate experimental animals has raised the possibility of drug action at each level of the female reproductive system. The early suggestion that THC may have a direct "estrogen-like" action on the uterus has not been substantiated by subsequent investigations indicating that THC does not interact with the estrogen cytoplasmic receptor. Since receptor recognition is a fundamental requirement for hormone action, it is unlikely that THC acts as an estrogen. The experiments suggesting such action should be repeated under conditions where the potential confounding effects of steroids secreted from non-gonadal sources are controlled. Direct ovarian effects of THC on the ovulatory process in the rodent as well as on steroid secretion from the cells of both the corpus luteum and the preovulatory follicle have been demonstrated. Whether these effects have significance with respect to physiological function remains a question, however, in view of the rather pronounced effects of cannabinoids on the secretion of those pituitary hormones regulating these ovarian events. Only additional investigation in vivo of the more subtle gonadal effects of THC treatment can clarify this issue. With respect to the pituitary hormones, there is clear evidence for the profound effects of cannabinoid exposure, of which the most pronounced may be those on the secretion of LH and prolactin. Effects on these reproductive hormones carry the threat of potential disturbance of the reproductive process, especially in the female where there is great dependence upon the appropriate cyclic changes in hormone levels. The full biologic impact of the pituitary effects of cannabinoids requires careful and thorough assessment. It can be concluded with reasonable confidence that THC alters the secretion of the pituitary reproductive hormones, and that of ACTH as well, through actions in the brain. While it would be reasonable to suggest that this site of action may reside in the MBH, the region of the hypothalamus most intimately associated with pituitary function, that does not seem to be the case for effects on prolactin and ACTH. Prevention of the expression of THC effects on these hormones by MBH deafferentation points to a more distant site for THC action. Some of the more likely possible sites for THC inhibition of prolactin secretion have been investigated, but direct evidence for their involvement was not forthcoming.

Pharmacology • December 1983

**Effects of delta 9-tetrahydrocannabinol, cannabinal and cannabidiol on the immune system in mice. II.
In vitro investigation using cultured mouse splenocytes**

Baczynsky WO, Zimmerman AM.

<http://www.ncbi.nlm.nih.gov/pubmed/6298842>

The effects of the cannabinoids, delta 9-tetrahydrocannabinol (THC), cannabinal (CBN) and cannabidiol (CBD), on the primary-like immune response were investigated in primary cultures of mouse splenocytes.

THC (1 and 5 microM) and CBD (5 microM) depressed the primary-like immune response of stimulated mouse splenocytes when incubated for the first 24 h after antigenic stimulation and the entire 6-day culture period. CBN did not show any measurable suppression of the primary-like immune response. Treatment of splenocyte cultures with cannabinoids after the first 24 h after antigenic stimulation showed no impairment of the in vitro primary-like immune response.

Journal Of Clinical Pharmacology • August 1981

Hypnotic and antiepileptic effects of cannabidiol

Carlini EA, Cunha JM.

<http://www.ncbi.nlm.nih.gov/pubmed/7028792>

Clinical trials with cannabidiol (CBD) in healthy volunteers, insomniacs, and epileptic patients conducted in the authors' laboratory from 1972 up to the present are reviewed. Acute doses of cannabidiol ranging from 10 to 600 mg and chronic administration of 10 mg for 20 days or 3 mg/kg/day for 30 days did not induce psychologic or physical symptoms suggestive of psychotropic or toxic effects; however, several volunteers complained of somnolence. Complementary laboratory tests (EKG, blood pressure, and blood and urine analysis) revealed no sign of toxicity. Doses of 40, 80, and 160 mg cannabidiol were compared to placebo and 5 mg nitrazepam in 15 insomniac volunteers. Subjects receiving 160 mg cannabidiol reported having slept significantly more than those receiving placebo; the volunteers also reported significantly less dream recall; with the three doses of cannabidiol than with placebo. Fifteen patients suffering from secondary generalized epilepsy refractory to known antiepileptic drugs received either 200 to 300 mg cannabidiol daily or placebo for as long as 4.5 months. Seven out of the eight epileptics receiving cannabidiol had improvement of their disease state, whereas only one placebo patient improved.

British Journal Of Clinical Pharmacology • June 1978

Bronchodilator effect of delta 1-tetrahydrocannabinol

Hartley JP, Nogrady SG, Seaton A.

Full text is available as a scanned copy of the original print version

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1429361/>

Delta1-trans-tetrahydrocannabinol, (delta1-THC) produces bronchodilatation in asthmatic patients. Administered in 62 microliter metered volumes containing 50-200 microgram by inhalation from an aerosol device to patients judged to be in a steady state, it increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1). The rate of onset, magnitude, and duration of the bronchodilator effect was dose related.

Advanced Drug Research • January 1977

Potential therapeutic agents derived from the cannabinoid nucleus

Pars HG, Howes JF.

<http://www.ncbi.nlm.nih.gov/pubmed/24325>

Drugs derived from *Cannabis sativa* (Cannabaceae) were used until the 1940's for their stimulant and depressant effects for treating somatic and psychiatric illnesses. Renewed interest in marijuana research began in the 1970's and again pointed to the therapeutic potential of cannabinoids. Safer and more useful therapeutic agents may be generated from cannabinoids similarly to morphine, lysergic acid diethylamide, and cocaine which have structurally related analgesics, oxytoxics, and local anesthetics respectively. It has been shown that the C-ring in cannabinoids can be substituted with a variety of nitrogen and sulfur-containing rings without loss of CNS (central nervous system) activity. Cannabinoids have been shown to inhibit prostaglandin synthesis, intensify pressor effects of endogenous amines like norepinephrine, and enhance the stimulant effects of amphetamine. Cannabinoids' therapeutic potential lies in the areas of analgesics and anticonvulsants, and for use as a sedative-hypnotic, an antiglaucoma agent, an antiasthmatic agent, an antidiarrheal agent, and possibly as an anticancer and immunosuppressant agent.

Thorax • December 1976

Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients

Williams SJ, Hartley JP, Graham JD.

Full text is available as a scanned copy of the original print version

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC470501/>

Ten volunteer inpatient asthmatics in a steady state were given a single inhalation of an aerosol (63 ml) delivered in random order, on each of three consecutive days, in the laboratory of a respiratory unit. Before, and for one hour after treatment the pulse, blood pressure (lying and standing), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak flow rate (PFR), and self-rating mood scales (SRMS) were recorded. Treatments were placebo-ethanol only; delta1-tetrahydrocannabinol (THC) 200 mug in ethanol; or salbutamol 100 mug (Ventolin inhaler), administered double blind. Salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were undetectable by radioimmunoassay. The mode of action of THC differs from that of sympathomimetic drugs, and it or a derivative may make a suitable adjuvant in the treatment of selected asthmatics.

Clinical Pharmacology And Therapeutics • December 1976

Influence of cannabidiol on secobarbital effects and plasma kinetics

Dalton WS, Martz R, Rodda BE, Lemberger L, Forney RB.

<http://www.ncbi.nlm.nih.gov/pubmed/791563>

To investigate the possible metabolic interaction between cannabidiol (CBD) and secobarbital, 6 male volunteers received 150 mg/70 kg sodium secobarbital orally immediately after smoking a marijuana cigarette prepared to deliver 0, 150, or 500 mug/kg CBD. The study was performed in a double-blind manner with each of the three treatments being assigned to every subject. Clinical effects and plasma secobarbital concentrations were recorded at periodic intervals. CBD did not alter the summary parameters which describe the secobarbital plasma concentration time curve. Secobarbital half-life, peak concentration, time of peak concentration, and area under the curve were unchanged by the coadministration of CBD. Clinical effects of secobarbital were also unaltered by CBD pretreatment. Thus at the doses administered, CBD does not appear to inhibit secobarbital metabolism in man.

The influence of delta9-tetrahydrocannabinol, cannabiol and cannabidiol on tissue oxygen consumption

Chiu P, Karler R, Craven C, Olsen DM, Turkanis SA.

<http://www.ncbi.nlm.nih.gov/pubmed/1197914>

The mechanism of the hypothermia produced in mice by the naturally occurring cannabinoids, delta9-tetrahydrocannabinol, cannabiol, and cannabidiol, was investigated by evaluating the direct effect of these drugs on the oxygen consumption of tissue homogenates and isolated mitochondria. The tissues studied were brain, liver, skeletal muscle, and heart; the mitochondrial preparations were limited to brain and skeletal muscle. The in-vitro studies included a description of the influence of various cannabinoid vehicles containing Tween 80, ethanol, Pluronic F68, and albumin on the oxygen consumption of tissue preparations. Of these vehicles, only albumin was without effect on all tissues. The other vehicles produced diverse responses, including some that were qualitatively different; the data illustrate that the influence of each vehicle on oxygen consumption must be defined for each tissue employed. In spite of the different vehicle effects, delta9-tetrahydrocannabinol generally reduced oxygen consumption of all tissue preparations; however, the vehicles were capable of modifying the dose-effect relationship. The results of all three drugs prepared in Pluronic F68 on brain and skeletal muscle indicated that the cannabinoids generally cause a dose-related depression of oxygen consumption. The findings demonstrate that the cannabinoids can directly decrease oxidative metabolism of tissue and isolated mitochondria and that a marked response occurs in the concentration range of 1×10^{-5} to 1×10^{-4} M. Because these concentrations can exist in tissues following the in-vivo administration of delta9-tetrahydrocannabinol, the results suggest that the depressant effect of the cannabinoids on metabolic rate may contribute to the mechanism of the hypothermia produced by the drugs.

Archives Of General Psychiatry • June 1975

Marihuana and setting

Hollister LE, Overall JE, Gerber ML.

www.archpsyc.jamanetwork.com/article.aspx?articleid=491378

Marihuana or placebo cigarettes were smoked by 12 subjects in two environments, one "favorable" and one "neutral". The object was to determine the contribution of setting to the effects reported from the drug. Two quantifiable self-report measurements, the linear euphoriant scale and the card-sort version of the Addiction Research Center Inventory (marihuana and hallucinogen scales), were the major reporting criteria. Analyses of variance consistently demonstrated strong effects for subjects and drug but not for the environmental conditions. Reports of marihuana effects may be assumed to be highly colored by psychological differences in the mental set of subjects, or biological variations in their responses to the drug. The actual environment in which the drug is taken seems to play little, if any, role.

JAMA Psychiatry • February 1, 1972

The Marihuana Tax Act of 1937

David F. Musto, MD

<http://archpsyc.jamanetwork.com/article.aspx?articleid=490581>

The anti-marihuana law of 1937 was largely the federal government's response to political pressure from enforcement agencies and other alarmed groups who feared the use and spread of marihuana by "Mexicans." Recent evidence also suggests that the Federal Bureau of Narcotics resisted the enforcement burden of the antimarihuana law until mounting pressure on the Treasury Department led to a departmental decision, probably in 1935, to appease this fear, mostly in the Southwest and West, by federal legislation. Previously unpublished documents clarify the role of medical research in the campaign for a federal anti-marihuana law and in the Treasury Department's preparation for congressional hearings.

Journal Of The American Chemical Society • April 1964

Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish

Y. Gaoni, R. Mechoulam

In lieu of an abstract, this link is to the original document in Jpeg format.

www.pubs.acs.org/doi/abs/10.1021/ja01062a046

END NOTES



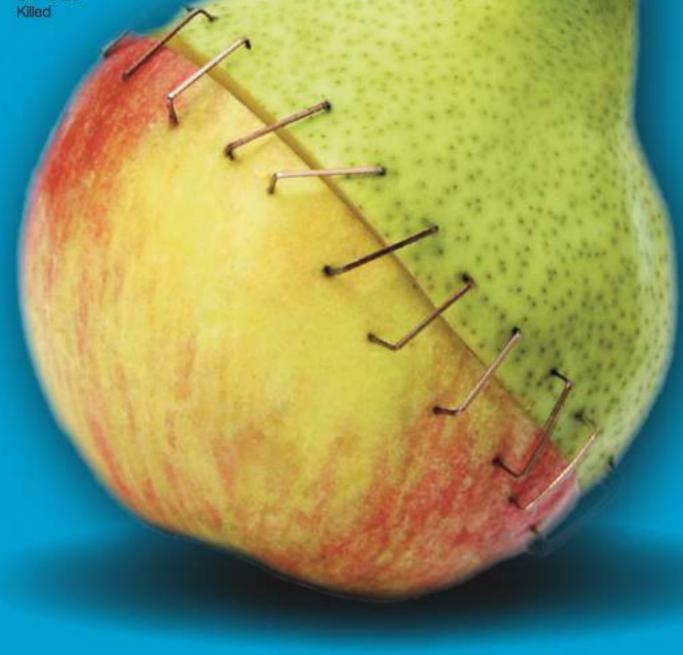
Smoking marijuana as a teenager can cause severe neurological disorders later in life.
One might become a sociopath and commit mass murder on a global scale.
Don't allow your children to smoke marijuana or this could happen to them.

BULLETPROOF

Another Jeff Prager Learning Experience • NoQ2015

Proving Monsanto's Crimes

The Serious GMO Dangers And Related Pesticide Neural Disorders And The Truly Unimaginable: The Murders, the Millions Murdered For Profit And The Millions Still To Be Killed



Silent Partners

Over 7 Billion Humans Have Been Colonized By Bacteria - Not A Shot Fired

by Jeff Prager

Even the British Empire had nothing on gut bacteria. The successful is a largely untold story to simply live. A number of bacteria. Exactly, from a remain alive without over 400 different but we'll stick to the in the digestive tract. od health and others they actively assist

Bacteria

ly bacteria in the up-ramful bacteria and use, an enzyme im-Involved in the pro-

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the bacteria mostly beneficial species that arepenes, L. brevis, ke acidophilus, one b vitamins and other



The Benefits Of Probiotics

We don't even know if probiotics work. We don't know if they manufacture our needed B vitamins, including niacin, pyridoxine, folic acid, and biotin. We don't know if they enhance our immune system activity. We don't know if antibacterial substances that kill or deactivate hostile disease causing bacteria actually work at all. Friendly bacteria do this by changing the local levels of acidity, by depriving pathogenic bacteria of their nutrients, or by actually producing their own antibiotic substances, yet we don't know if drinking kefir, eating pickles and sauerkraut or ingesting probiotics even works. We don't know if the ingested bacteria builds a house on your intestinal wall, so to speak, and lives in your gut for a day, a week, a month or forever or whether they take the next gut-wrenching feces train to Sewer City, USA on the Toilet Express. Honestly, we're clueless. But we think it helps.

Gut Bacteria

by Jeff Prager

Gut microorganisms benefit the host by gleaming the energy from the fermentation of undigested carbohydrates and the subsequent absorption of short-chain fatty acids. The most important of these fatty acids are:

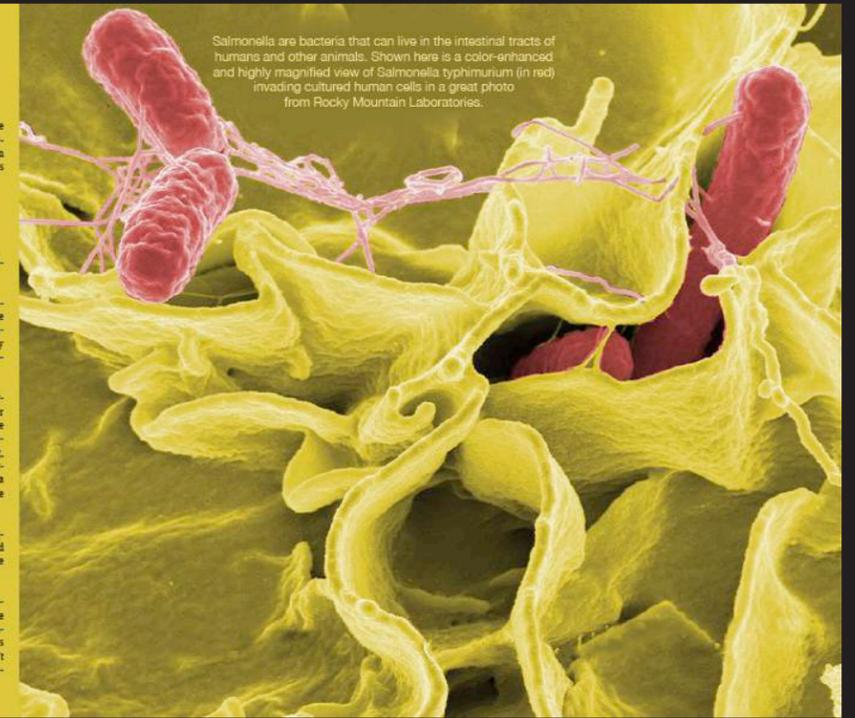
- Butyrates, metabolized by the colonic epithelium
- Propionates metabolized by the liver
- and acetates metabolized through the action of muscle tissue

Intestinal bacteria also play a role in synthesizing vitamin B and vitamin K as well as metabolizing bile acids, sterols, and xenobiotics. Xenobiotics are typically a synthetic chemical that is foreign to the body or in some cases to an entire ecological system. Xenobiotics are intestinal janitors.

The human body carries about 100 trillion microorganisms in its intestines, a number ten times greater than the total number of human cells in the body. The metabolic activities performed by these bacteria resemble those of an actual organ like a heart or a lung, leading some to liken gut bacteria to a "forgotten" organ. It's estimated that these gut flora have around a hundred times as many genes in aggregate as there are in the human genome.

Our microbiota so very obviously play a large, significant and unquestionably necessary part in good human health and a part we still know very little about.

As a species we human beings are rapidly developing a new genera of immunosible and often times rare disorders manifesting with such intrusive and unimaginably odd neurological symptoms such that it's a wonder all approximately 305 million of us aren't already on the verge of a completely and swiftly disabling disorder.



Salmonella are bacteria that can live in the intestinal tracts of humans and other animals. Shown here is a color-enhanced and highly magnified view of Salmonella typhimurium (in red) invading cultured human cells in a great photo from Rocky Mountain Laboratories.



STAPHYLOCOCCUS AUREUS

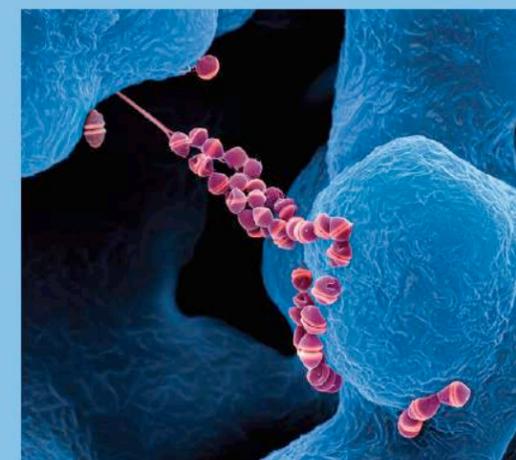
of us. But it can turn rogue, causing skin infections—or worse. century has prompted the evolution of deadly superbug strains. erium that is a member of the Firmicutes, and is frequently found ure for catalase and aureum reduction. Although S. aureus is not actions (e.g. boils), respiratory disease (e.g. sinusitis), and food

poisoning. Disease-associated strains often promote infections by producing potent protein toxins, and expressing cell-surface proteins that bind and inactivate antibodies. The emergence of antibiotic-resistant forms of pathogenic S. aureus (e.g. MRSA) is a worldwide problem in clinical medicine.



MOUTH MICROBES

The human mouth hosts a panoply of microbes, some taking up residence on the mouth lining (blue) within days after birth. Harmful species form biofilms, like the plaque that encourages tooth decay, or colonize the crevices between teeth and gums, causing periodontal disease. Oral probiotics designed to boost the population of species that outcompete pathogenic ones could help prevent or reverse dental disease. Researchers (very patient researchers) have painstakingly harvested all the plaque from every surface of every tooth. It weighs, on average, about 10 mg. But the teeth only comprise 1/20 of all the oral surfaces. You have to multiply the 10 mg from the teeth by 20 to get the total biomass including cheeks, tongue, etc. We also know that 1 mg of oral biomass typically contains about 100 million microbes. By multiplying the number of microbes in 1 mg by 20, we get the total number of microbes in the entire oral cavity: 100 million microbes x 20 mg biomass = 20 billion oral microbes living in your mouth right now. Almost all of those billions of microbes that we swallow began their lives in an oral biofilm. Thus, despite only having (at any given time) 20 billion microbes in our mouths, we nevertheless swallow 100 billion! Five times more than we have. So, those 20 billion microbes in our mouths must be producing and shedding 100 billion additional microbes every day. That's five times their original number. Said another way, they are dividing five times every 24 hours. Dividing 24 hours by 5 = 4.8 hours, the amount of time it takes for the microbes in our mouths to double their number. There are 20 billion bacteria in your mouth and they reproduce every five hours. If you go 24 hours without brushing, those 20 billion become 100 billion!



STREPTOCOCCUS

A colorized electron microscope image captures delicate chains of streptococcus in a laboratory sample. Though some strep infections can be deadly, many strains are harmless—among the thousands of benign beings that make their home in our bodies. Most Streptococcus genomes are 1.8 to 2.3 Mb in size and encode 1,700 to 2,300 proteins. There are two types of Strep: group A and group B. Group A strep causes Strep throat - a sore, red throat, sometimes with white spots on the tonsils; Scarlet fever - an illness that follows strep throat. It causes a red rash on the body; Impetigo - a skin infection; Toxic shock syndrome; Cellulitis and necrotizing fasciitis (flesh-eating disease). Group B strep can cause blood infections, pneumonia and meningitis in newborns. A screening test during pregnancy can tell if you have it. If you do, IV antibiotics during labor can save your baby's life. Adults can also get group B strep infections, especially if they are elderly or already have health problems. Strep B bacteria can cause urinary tract infections, blood infections, skin infections and pneumonitis in adults.



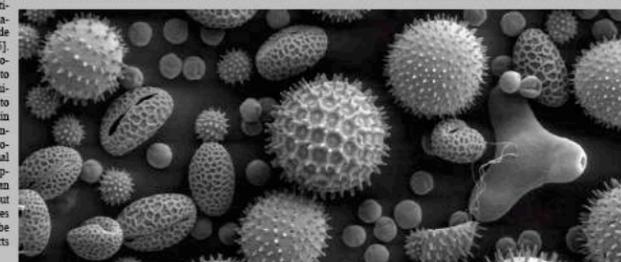
HELICOBACTER

Helicobacter pylori (yellow), a common bacterium that lives in the stomach lining, increases the risk of stomach cancer (brown cells) and peptic ulcers. But over time H. pylori can reduce stomach acid and acid reflux, which may help fend off esophageal cancer. The microbe also appears to help protect us from allergies and asthma. Some scientists suspect that the dramatic increase in those conditions in those colonized in the industrialized world could be related to the decreasing frequency of H. pylori in our stomachs, which is partly due to high doses of antibiotics in childhood. Helicobacter pylori is a Gram-negative, microaerophilic bacterium found in the stomach, and may be present in other parts of the body, such as the eye. It was identified in 1982 by Australian scientists Barry Marshall and Robin Warren with further research led by British virologist Stewart Gordon, who found that it was present in patients with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. However, over 80% of individuals infected with the bacterium are asymptomatic and it may play an important role in the natural stomach ecology.

metabolism is poorly understood but appears to involve transport to the liver by the portal circulation. It is believed that SCFAs also impact water absorption, local blood flow, and epithelial proliferation in the large intestine [9].

Genomic analysis of gut bacteria offers vivid examples of the role of microbes in nutrient utilization. For example, in 2003, Xu, et al. published the complete genome sequence of the gram-negative anaerobe Bacteroides thetaiotaomicron, a prominent member of the normal intestinal microbiota [10]. Annotation and analysis of the genome revealed a sophisticated apparatus for acquiring and digesting otherwise unusable dietary polysaccharides. This apparatus, including a complex, multi-component, multi-enzyme complex starch utilization system (SUS), consists of over 230 glycoside hydrolase and 15 polysaccharide lyase genes [15]. The genomic analysis demonstrated that B. thetaiotaomicron has evolved the remarkable capacity to sense the availability of carbohydrates in its microenvironment, and that it also has the ability to forage and utilize host-derived glycans (e.g., mucin and heparan). Mechanistic studies in gnotobiotic animals further demonstrated that, when B. thetaiotaomicron senses a scarcity of fucose in the intestinal lumen, it actually induces the gut epithelium to up-regulate expression of fucosylated glycans that can be used by the bacteria as an energy source without harming the host [16]. This body of work illustrates how the remarkable host-microbe symbiosis can be teased apart by pairing genomic sequencing efforts with creative in vivo laboratory studies.

Microbiota and Protein Metabolism



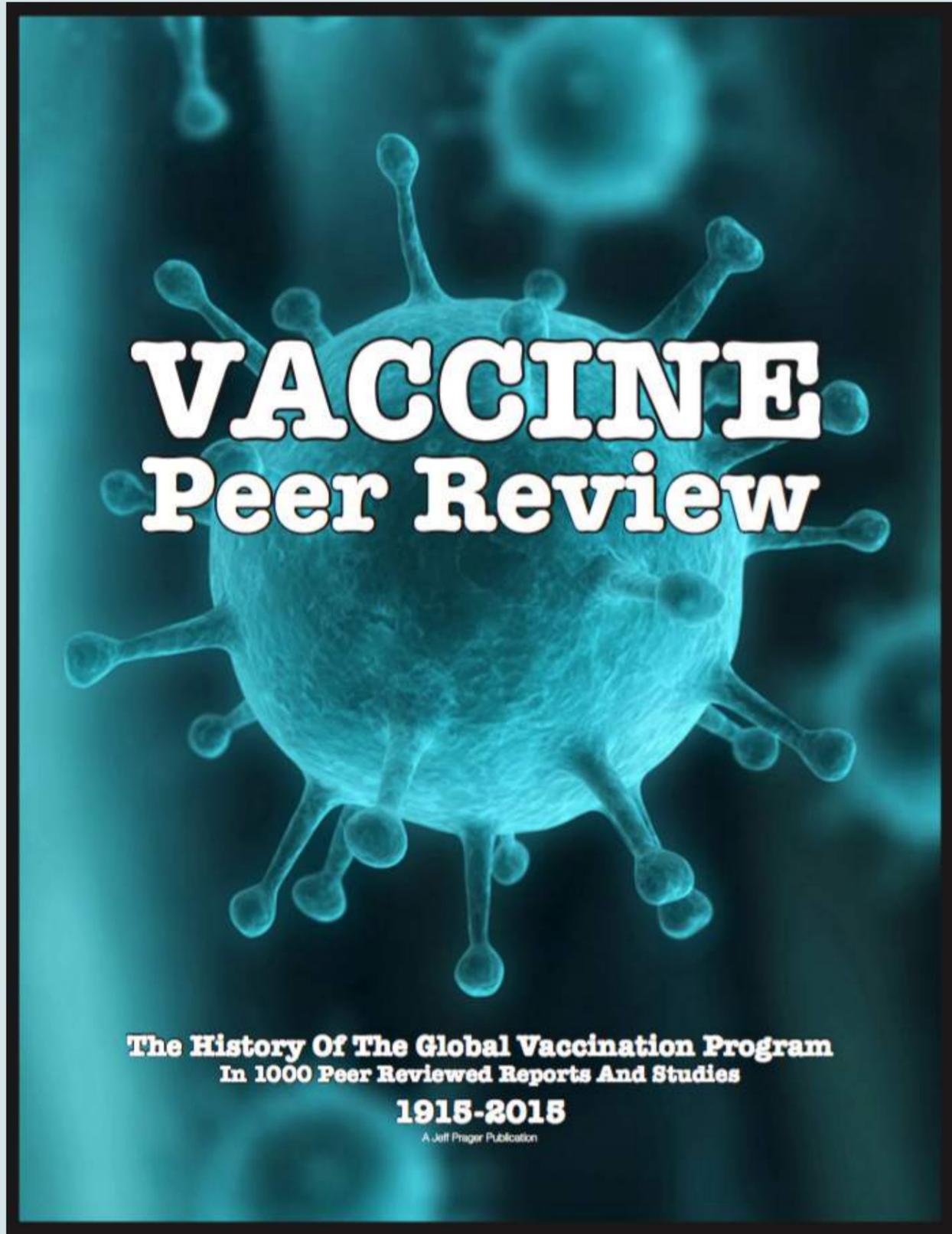
amino acids. More work is needed to define these contributions in both healthy and undernourished humans. The intestinal microbiota also contributes to nitrogen balance by participating in urea nitrogen salvaging (UNS) [21, 22]. Elevated urease expression in gut microbes results in metabolism of urea in the GI tract into ammonia and carbon dioxide. Some of the ammonia can be utilized for microbial synthesis of amino acids. Perhaps more importantly, the nitrogen generated during this process (urea nitrogen) can re-enter the host circulation and serve as a substrate for synthetic processes [23]. Interestingly, reduced urea recycling has been reported in GF animals [24] and in humans receiving antibiotic therapy [25]. Furthermore, several reports indicate that regulation of UNS is important in settings of low N intake and high N demand (e.g., during pregnancy and during periods of rapid somatic growth in infancy) [26–28]. While still relatively preliminary, these studies underscore the relationship between gut microbes and protein metabolism that will likely be further described through on-going characterization of the human microbiome.

MICROBIOTA AND LIPID METABOLISM

Until recently few studies of the association between lipid metabolism and the microbiome existed. However, important research by Jeffrey Gordon, Fredrick Backhed, and colleagues suggests that the body's supply of triglycerides, a prominent source of energy during critical illness [29], is tightly linked to the intestinal microbiota. These findings have enormous potential relevance for research in a wide range of disease states, including metabolic disorders such as obesity (see below) and cardiovascular disease.

100's Of Peer Reviewed Reports On Monsanto's Glyphosate

<https://drive.google.com/file/d/0B3mMkPwF1DUPWDINV3ICdk5RX0U/view?usp=sharing>



“There is a great deal of evidence to prove that immunization of children does more harm than good”

Dr. J. Anthony Morris, former Chief Vaccine Control Officer, FDA

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2. Many commonly used brominated and chlorinated flame retardants can undergo long-range environmental transport.

3. Many brominated and chlorinated flame retardants appear to be persistent and bioaccumulative, resulting in food chain contamination, including human milk.

4. Many brominated and chlorinated flame retardants lack adequate toxicity information, but the available data raises concerns.

5. Many different types of brominated and chlorinated flame retardants have been incorporated into products even though comprehensive toxicological information is lacking.

6. Brominated and chlorinated flame retardants present in a variety of products are released to the indoor and outdoor environments.

7. Near-end-of-life and end-of-life electrical and electronic products are a growing concern as a result of dumping in developing countries, which results in the illegal transboundary movement of their hazardous constituents. These include brominated and chlorinated flame retardants.

8. There is a lack of capacity to handle electronic waste in an environmentally sound manner in almost all developing countries and countries with economies in transition, leading to the release of hazardous substances that cause harm to human health and the environment. These substances include brominated and chlorinated flame retardants.

9. Brominated and chlorinated flame retardants can increase fire toxicity, but their overall benefit in improving fire safety has not been proven.

10. When brominated and chlorinated flame retardants burn, highly toxic di-

oxins and furans are formed.

11. Therefore, these data support the following:

12. Brominated and chlorinated flame retardants as classes of substances are a concern for persistence, bioaccumulation, long-range transport, and toxicity.

13. There is a need to improve the availability of and access to information on brominated and chlorinated flame retardants and other chemicals in products in the supply chain and throughout each product's life cycle.

14. Consumers can play a role in the adoption of alternatives to harmful flame retardants if they are made aware of the presence of the substances, for example, through product labeling.

15. The process of identifying alternatives to flame retardants should include not only alternative chemicals but also innovative changes in the design of products, industrial processes, and other practices that do not require the use of any flame retardant.

16. Efforts should be made to ensure that current and

alternative chemical flame retardants do not have hazardous properties, such as mutagenicity and carcinogenicity, or adverse effects on the reproductive, developmental, endocrine, immune, or nervous systems.

17. When seeking exemptions for certain applications of flame retardants, the party requesting the exemption should supply some information indicating why the exemption is technically or scientifically necessary and why potential alternatives are not technically or scientifically viable, a description of potential alternative processes, products, materials, or systems that eliminate the need for the chemical, and a list of sources researched.

18. Wastes containing flame retardants with persistent organic pollutants (POP) characteristics should be managed in a way that prevents POPs from being released to the environment.

19. Flammable and unbleached cotton more but rest longer too, especially pillowcase and doily of people have, of natural materials or down, for washable may be greater but plastic shower from new plastic

20. It may be able to sell PBDE from furniture since vacuum your bed-linens every week, on is to simply air opening your windows fresh air inside can once in a while, even and sunny, take sitting in the sun

21. It is also important to avoid using plastic and unbleached cotton more but rest longer too, especially pillowcase and doily of people have, of natural materials or down, for washable may be greater but plastic shower from new plastic



POPs SKULKING AROUND THE HOUSE

Original from: <https://www.epa.gov/pesticides/pesticides-program/pesticides-education>

Daddy, There's A Monster In My Room

200 Peer Reviewed Reports And Studies Describing The Numerous Health Dangers Associated With The Human Body Burden Of Persistent Organic Pollutants
The Monsters In The Food, Air And Water



Daddy, There's A Monster In My Room

A Free PDF Paper Publication



Persistent Organic Pollutants • POPs THE PEER REVIEW

PERSISTENT ORGANIC POLLUTANTS: IN OUR BEDS, OUR CLOTHES, OUR HOMES, OUR SCHOOLS, OUR FOOD, OUR WATER, OUR AIR AND OUR SOIL

The Health Damage Associated With The Body Burden Of POPs And PBDEs In Pregnant Women, Newborns And Adults In 200 Peer Reviewed Reports & Studies

In the United States, PBDEs are marketed with trade names: DE-60F, DE-61, DE-62, and DE-71 applied to pentaBDE mixtures; DE-79 applied to octaBDE mixtures; DE 83R and Saytex 102E applied to decaBDE mixtures. The available commercial PBDE products are not single compounds or even single congeners but rather a mixture of congeners each denoted by its corresponding number. PBDE-209 is one of the most egregious human poisons.

Because they're mixed into plastics and foams and don't actually bind to them, PBDEs can leave the product that contains them and enter the environment—your home, the classroom, the day care center and anywhere else. They also enter the environment and are significant pollutants of our soil, rivers, streams and oceans.

Polybrominated-Biphenyl-Ethers or PBDE's are known for being hormone disruptors which can accumulate in the placentas and even contaminate a mother's breast milk. Another danger connected to these compounds is the fact that they aren't biodegradable. They accumulate in the air



POPs CAN EVEN SNEAK INTO YOUR CLOSET WHEN YOU AREN'T PAYING ATTENTION.

chemicals also, even more so because they're closer to the ground, and from an unimaginable number of sources every day primarily because small children put things in their mouths. The peer review helps us understand the dangers of chemical exposure in the day care environment. For this reason alone it's imperative that you shield your children from obvious, easily avoidable and very dangerous chemicals without affecting their ability to enjoy their playtime, friends and youth.

Get rid of any pillows and mattresses that are at least 2 years old. Replace any hypoallergenic pillow stuffed with synthetic fiber and get untreated pillows that are made out of feathers or wool. If allergies are a concern, you can opt for a pillow made out of latex foam. There are many available on the internet. Consider organic mattresses that are either made up of naturally fire retardant wool, organic cotton and coils that are free of formaldehyde. One brand is the Greenpeace brand. I've never used it but I know it's a quality product.

Wash your bedding and unbleached cotton more but rest longer too, especially pillowcase and doily of people have, of natural materials or down, for washable may be greater but plastic shower from new plastic. It may be able to sell PBDE from furniture since vacuum your bed-linens every week, on is to simply air opening your windows fresh air inside can once in a while, even and sunny, take sitting in the sun.

Formaldehyde-based resins are used as adhesives and resins in the manufacture of particle-board, plywood, furniture, kitchen cabinets and other wood and simulated wood products. It's also used for the production of material like appliances, electric controls, telephones, wiring services and it's used in the textile, leather, rubber and cement



for a couple of hours. This will ventilate the mattress and allow for evaporation of some Persistent Organic Pollutants and result in a cleaner mattress.

In view of its widespread use, toxicity and volatility, exposure to formaldehyde is also a significant consideration for health. Formaldehyde is known to cause tiredness, insomnia, headaches, coughing and skin irritation. In June 10, 2011, the US National Toxicology Program described formaldehyde as "known to be a human carcinogen".

Formaldehyde-based resins are used as adhesives and resins in the manufacture of particle-board, plywood, furniture, kitchen cabinets and other wood and simulated wood products. It's also used for the production of material like appliances, electric controls, telephones, wiring services and it's used in the textile, leather, rubber and cement

industries. Other uses are as binders for foundry sand, stone wool and glass wool mats in insulating materials, abrasive paper and brake linings.

Dust furnishings regularly with a damp cloth and launder the cloth afterwards. Vacuum regularly and clean filters and discard bags before they're over-filled. Vacuums with a HEPA filter are most helpful. You might consider shampooing the carpet once a year. Wear only 100% cotton or wool clothing and always wash new clothing alone in the washer once with normal detergent and once again with water alone to fully rinse them. Avoid dry cleaning your clothing. Don't wear your shoes in the home. Wearing shoes in the house brings not just a host of microscopic chemicals inside but radiation as well. Best to leave all shoes in the foyer. Place them on a mat outside the front door before entering your home and don't allow others to wear shoes in your home either. Open windows year

around, even if just briefly and keep your home aired out sufficiently.

A study published in Environmental Health Perspectives in March of 2010 titled, "Polybrominated Diphenyl Ethers (PBDEs) and Hexabromocyclododecane (HBCD) in Composite U.S. Food Samples" by Schecter, et al., stated:

"Total PBDE concentrations in food varied by food type, ranging from 12 pg/g wet weight (ww) in whole milk to 1,545 pg/g ww in canned sardines and 6,211 pg/g ww in butter. Total HBCD concentrations also varied substantially within and among food groups, ranging from 23 pg/g in canned beef chili to 593 pg/g in canned sardines. HBCD was not detected in any dairy samples. Dietary intake of all PBDE congeners measured was estimated to be 30 ng/day, mostly from dairy consumption but also from meat and fish. HBCD intake was estimated at 16 ng/day, primarily from meat consumption. PBDEs and HBCDs currently contaminate some food purchased in the United States, although PBDE intake estimated in this study is lower than reported in our previous market basket surveys. HBCD is in food at higher levels than expected based on previously reported levels in milk and blood compared with PBDE levels and is comparable to European levels."

Not all flame retardants present concerns, but the following types often do:

- Halogenated flame retardants (also known as organohalogen flame retardants) containing chlorine or bromine bonded to carbon.
- Organophosphorous flame retardants containing phosphorous bonded to carbon.

For these types of flame retardants some are associated with health and environmental concerns, many are inadequately tested for safety and they provide questionable fire safety benefits as used in some products.

The major uses of flame retardant chemicals by volume in the U.S. are: Electronics, Building Insulation, Polyurethane foam and wire and cable manufacturing. These chemicals are persistent, they don't easily break down into safer chemicals in the environment

in your house, contributing to constant dust pollution in the home.

Write surrounded by chemicals all day, all the time, and our bodies are literally attacked all day, every day—not just by all sorts of bacteria but by the invisible environmental chemicals we all come into contact with. From automotive exhaust, perfumes, colognes and soaps, the unseen industrial pollution in the air we breathe, the indoor dust we're constantly surrounded by and even the food we eat—these are all contaminated with various neurotoxins, obesogens, mutagens, genotoxins, endocrine disruptors and carcinogens from flame retardants, Bisphenol analogues (A,B,S,F,AP), Pharmaceutical And Personal Care breakdown products and transformation products, and 100s of other massively produced chemicals that are now environmentally ubiquitous.

The peer review is clear, even the food is contaminated with industrial chemicals like Polybrominated Diphenyl Ethers and Persistent Organic Pollutants. Yet we all have, we hope, an active and robust immune system,

an effective internal supply of antioxidants and other functional systems within our bodies that fight these attacks effectively every moment of every day. If we didn't we'd be sick all the time, or worse. That doesn't mean these various 100s of chemicals won't eventually make us sick, and some of us are more susceptible than others, so we should all be aware of them and work proactively to avoid contact and mitigate our exposures and that of our children.

As of June 1, 2006 the State of California began prohibiting the manufacture, distribution, and processing of flame-retardant products containing pentabrominated diphenyl ether (pentaBDE) and octabrominated diphenyl ether (octaBDE). PBDEs are so pervasive in the environment that according to the EPA, exposure may pose health risks. According to U.S. EPA's Integrated Risk Information System, evidence indicates that PBDEs may possess liver toxicity, thyroid toxicity, and neurodevelopmental toxicity. In June 2008, the U.S. EPA set a safe daily exposure maximum of 7 ug per kg body weight per day for 4 most common 209 PBDEs.

In April 2007, the legislature of the state of Washington passed a bill banning the use of PBDEs. The State of Maine Department of Environmental Protection found that all PBDEs should be banned. In August, 2003, the State of California outlawed the sale of penta- and octa- PBDE and products containing them, effective January 1, 2008. In May 2007, the legislature of the state of Maine passed a bill phasing out the use of DecaBDE.

The European Union decided to ban the use of two classes of flame retardants, in particular, polybrominated diphenyl ethers (PBDE) and polybrominated biphenyls (PBBs) in electric and electronic devices. This ban was formalized in the RoHS Directive, and an upper limit of 1 g/kg for the sum of PBBs and PBDEs was set. In February 2009, the Institute for Reference Materials and Measurements (IRMM) released two certified reference materials (CRMs) to help analytical laboratories better detect these two classes of flame retardants. The reference materials were custom-made to contain all relevant PBDEs and PBBs at levels close to the legal limit.

At an international level, in May 2009 the Parties of the Stockholm Convention for Persistent Organic Pollutants (POP) took the decision to list commercial penta-BDE and commercial octa-BDE as POP substances. This listing is due to the properties of hexa-BDE (hexabromodiphenyl ether) and hepta-BDE (heptabromodiphenyl ether) which are the main components of commercial octa-BDE, and due to the properties of tetra-BDE (tetrabromodiphenyl ether) and penta-BDE (pentabromodiphenyl ether) which are the main components of commercial penta-BDE.

With 209 different congeners and extraordinary bio-persistence and environmental persistence, Persistent Organic Pollutants, POPs, like Polybrominated Diphenyl Ethers, PBDEs, aren't going away any time soon and the human body burden for those that don't become actively involved in simple mitigation procedures will likely increase in most areas via food and dust alone.

If you're raising children then you probably know that your children are exposed to a wide variety of



“ the authors intend to present ASIA, or Shoenfeld's syndrome, as an autoimmune syndrome induced by adjuvants ”

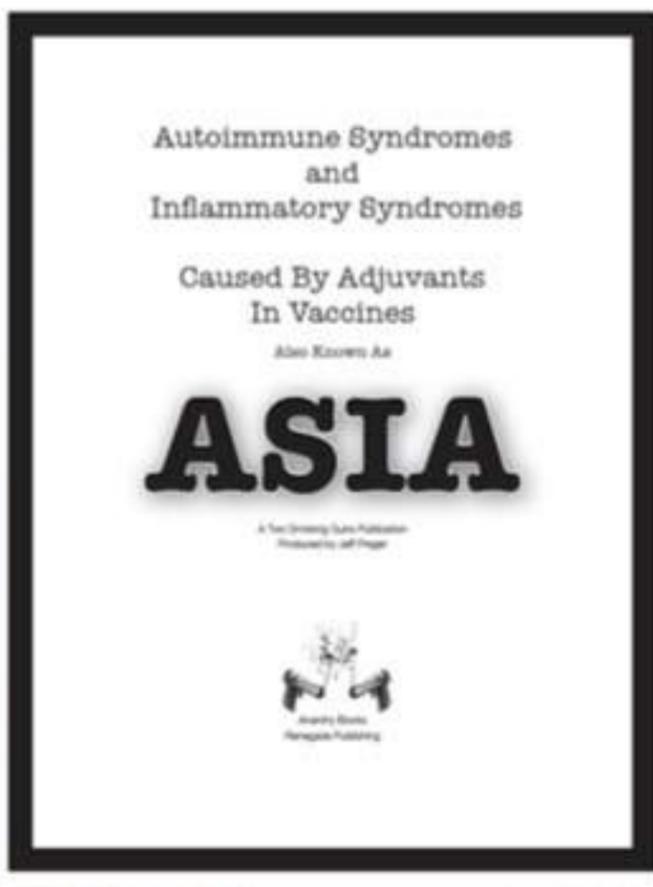
From the *European Journal of Internal Medicine* • July 2013
ASIA or Shoenfeld's syndrome an autoimmune syndrome induced by adjuvants
Eugene H. Chao B.
Abstract
Recently reports have suggested grouping different autoimmune conditions that are triggered by external stimuli as a single condition called autoimmune syndrome induced by adjuvants (ASIA). The condition is characterized by the appearance of multiple autoimmune disease conditions, including arthritis, chronic fatigue, sleep disturbances, cognitive and emotional and sensory loss, and the possible occurrence of a disseminating autoimmune disease caused by various exposure after vaccines and adjuvants. As there are no markers for ASIA, the authors intend to present ASIA, or Shoenfeld's syndrome, as an autoimmune condition induced by adjuvants.
<http://www.ejim.elsevier.com/abstract/S092464601300024>

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Annals of the New York Academy of Sciences • 2011
Behavioral effects of gestational exposure to aluminum
Kathrin L. Sedorella K., Clayton K., Manning A.
Institute of Cell, Animal and Population Biology, Edinburgh, UK
Abstract

The involvement of aluminum in the etiology of a number of human pathological diseases has attracted the attention from being a metabolic, neurotoxic, nephrotoxic element. This study of gestational exposure to the aluminum sulfate which is more susceptible to absorption at lower levels than the adult. Little attention has been given to reproductive toxicity until recently and further evaluation of its toxicity. Our preliminary results showed neurochemical alterations in the offspring during gestation. Further, the effects of such exposure on adult neural signaling processes changes to be observed.

...suggesting persistent behaviour following exposure ”



From the *Journal Frontiers in Neurology* • February 2017
Biopersistence and brain translocation of aluminum adjuvants of vaccines
Cherwell BK, Sial H, Colpence G, Aubert FJ, Cabannes J.
Faculté de Médecine and Faculté des Sciences et Technologies, Université Claude-Bernard Lyon 1, Université Paris-Est Créteil, Créteil, France
Abstract
Aluminum hydroxide sulfate is a crystalline compound widely used as an immunological adjuvant of vaccines. Concerns linked to the use of aluminum adjuvants following recognition of their covalent role in the so-called neurotoxic adjuvants (NMF) have attracted in patients with multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, MSMT revealed an unexpectedly long-lasting biopersistence of aluminum within immune cells in presumably susceptible individuals, showing the previous fundamental misconception of its biodegradability. We previously showed that poorly biodegradable aluminum-coated particles exposed into muscle are promptly phagocytosed at muscle and the resulting large vesicles, and are disseminated within phagocytic cells throughout the body and slowly translocate in brain. This strongly suggests that long-term adjuvant biopersistence within phagocytic cells is a prerequisite for slow brain translocation and delayed neurotoxicity. The understanding of basic mechanisms of particle biopersistence and brain translocation represents a major health challenge, since it could help to define neurotoxic factors in developing chronic neurotoxic damage. Biopersistence of aluminum may be linked to its lysosomal-dissolving effect, which is likely due to direct crystal-induced rupture of phagolysosomal membrane. Subsequently, this continuously persists foreign particles in their cytosol will slowly interact with various intracellular organelles, a diffusion front of autophagy (autophagy) until they disappear of aluminum materials. Successful compartmentalization of particles within double membrane autophagosomes and subsequent fusion with lysosomes and in acidified lysosomes will expose aluminum to lysosomal acidic pH, the rate factor that can stabilize aluminum particles. Brain translocation of aluminum particles is linked to a Trojan horse mechanism previously described for infectious particles (SVV, HCV), that steps on CD22, signaling the major inflammatory immune chemotaxis.
<http://www.frontiersin.org/abstract/10.3389/fnol.2017.00008>

“ This strongly suggests that long-term adjuvant biopersistence within phagocytic cells is a prerequisite for slow brain translocation and delayed neurotoxicity ”



“ These outcomes should raise concerns about the increasing use of Al salts as vaccine adjuvants ”



This extremely important peer reviewed report was published in 1991 by the Institute of Medicine (US).
The Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines in Washington DC.

The study was published in hard-cover by the National Academies Press. You got your copy or heard about it, right?

The findings of the study are:

"that the evidence is consistent with a causal relation between DPT vaccine and acute encephalopathy and shock and "unusual shock-like state," and between RA 27/3 rubella vaccine and chronic arthritis; and that the evidence indicates a causal relation between DPT vaccine and anaphylaxis, between the pertussis component of DPT vaccine and protracted, inconsolable crying, and between RA 27/3 rubella vaccine and acute arthritis."

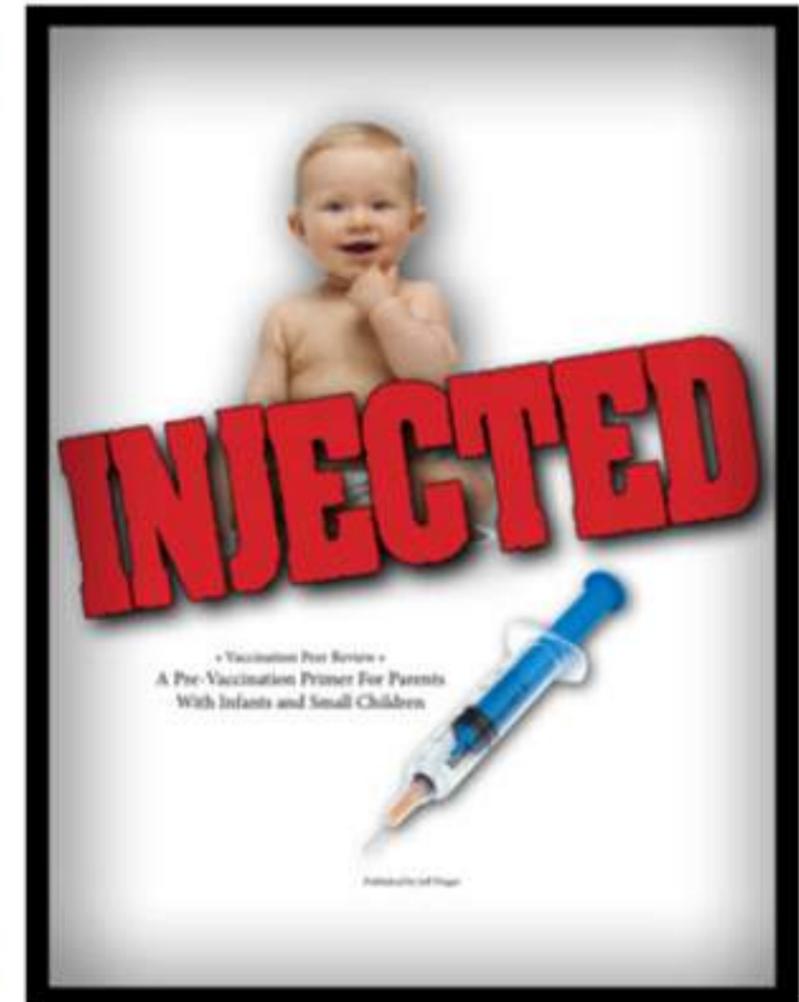
VACCINES

CAUSE

ACUTE ARTHRITIS

CHRONIC ARTHRITIS

AND INCONSOLABLE CRYING



Vaccines cause genetic damage and transgenerational disorders - The peer review

<https://drive.google.com/file/d/0B3mMkPwF1DUPdjh6Ukwya21jT0U/view?ths=true>



THE END