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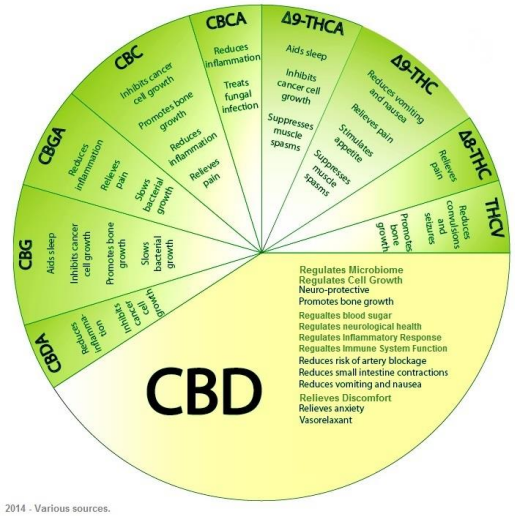
The Science, Law and Clinical Aspects of Cannabadiol Nutrition

THC and CBD in Clinical Practice



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Abstract: Δ(9)Tetrahydrocannabinol (THC) is found in Marijuana (Cannabis) plants in varying concentrations. It is a psychoactive and neurotoxic phyto cannabinoid which has recently garnered significant attention for reputed clinical benefits. Although its legal status is evolving, it is still a Schedule 1 drug in international conventions and, thus, in many jurisdictions.

In contrast, Cannabadiol (CBD) is a nutrient found both in the body and in some varieties of Cannabis. It is not, and never has been, a Schedule 1 drug and it is lawful to possess, trade or use.

As endo-CBD, it is a normal constituent of the mammalian neurotransmitter system; as phyto-CBD it is found in Industrial Hemp (the correct name for low THC, high CBD cannabis) and other plants. Supplementing the diet with CBD has significant health benefits.

Important Note: The authors want to make it absolutely clear that while the evidence convinces us that CBD is both safer and more effective in every clinical category of use, we also believe in absolute health freedom, which means that each person has complete dominion over his/her body so that if he/she choses to use the more in*toxic*ating and less effective THC compounds or synthetics rather than the safer, more effective CBD nutrient compounds, that is an inalienable right.

From a physiological and medical standpoint, however, we believe that the healthy hemp future is with CBD while the recreational future continues with THC.

Section 1: Historical and Legal Background
THC is a Schedule I Drug; CBD is *Not*

Now that 23 US States and the District of Columbia have defied long-standing FDA/DEA policy and, asserting Ninth and Tenth Amendment protections, rebelliously legalized some form (or, in some cases, all forms) of marijuana or hemp growing and use, opportunity, emerging science, pseudoscience and confusion reign.

We believe that it is essential to

1. Define the current legal status of THC and examine the dearly held, but not necessarily accurate, belief that THC, the psychoactive moiety of marijuana or hemp, is both safe and necessary for *medical* purposes. That it is widely desired for *recreational* purposes is undeniable and outside the scope of our consideration here.

2. Define the current legal status and examine the health uses of CBD, the non-psychoactive moiety of Cannabis or hemp, which is both safe and necessary for the purposes of achieving and maintaining a healthy status.

3. Define and examine the evidence concerning the health use of

a. High THC
b. High THC/High CBD
c. High THC/Low CBD
d. High CBD/Low THC
e. High CBD

THC, both legal and illegal, has long been unquestionably 'sexy' as a symbol of defiance, a medicinal herb, recreational molecule and a hot new, sometimes-legal, investment. Despite interstate boundary restrictions, its cultivation and processing has rapidly become a vigorous market sector in the US.

The recent Federal decision by the US Congress not to fund DEA raids on State licensed dispensaries heralds a major sea change from the vicious and irrational persecution of victimless crimes leading to fully 25% of the immense US prison population being incarcerated for victimless crimes related to marijuana or hemp.

Cannabis has a long history of human use as a euphoriant and medicinal herb first documented in a Chinese medical manuscript considered to originate in 2737 BC.[1]

Its use gradually spread from China to Europe, reaching Europe by about 500 AD.

In both Colonial America and the US during World War II, hemp was cultivated for its fiber and found to have a vast numbers of uses.

The *US Pharmacopeia* listed hemp from 1850 through 1942 for indications including labor pains, nausea, and rheumatism. It was also commonly used as an intoxicant from 1850 to about 1930 in the US. At that time, a vigorous campaign was conducted by the U.S. Federal Bureau of Narcotics (then the Bureau of Narcotics and Dangerous Drugs [BNDD] now the Drug Enforcement Agency [DEA])[2] to depict hemp/marijuana as a powerful, addicting substance leading users into narcotics addiction, leading to Marijuana/hemp in any form being outlawed and the destruction of the large US industrial hemp industry.

Some authorities still consider marijuana a "gateway" drug, though that position has little, if any, substantiation.[3]

[1] http://www.infoplease.com/encyclopedia/science/marijuana-history-marijuana-use.html
[2] The Drug Enforcement Administration was created by President Richard Nixon through an Executive Order in July 1973 in order to establish a single unified command to combat "an all-out global war on the drug menace." At its outset, DEA had 1,470 Special Agents and a budget of less than $75 million. Today, the DEA has nearly 5,000 Special Agents and a budget of $2.02 billion. http://www.dea.gov/about/history.shtml
[3] http://en.wikipedia.org/wiki/Gateway_drug_theory

During the 1950s marijuana took on powerful counter-cultural association as a tool of rebellion of the "beat generation" while in the 1960s it was used as a symbol of rebellion against authority by protestors, "hippies" and disaffected college students.

In 1970, the US criminalized marijuana use, possession and sale by making it, along with LSD, a Schedule I drug[4]

In 1971, the United Nations superseded its 1961 *Single Convention on Narcotic Drugs*[5] with the *Convention on Psychotropic Substances.*[6] This United Nations treaty (which supersedes national law among the signatories of the Convention) was designed to control psychoactive, rather than toxic, drugs such as amphetamine, barbiturates, benzodiazepines and Δ(9)Tetrahydrocannabinol (THC). The Convention, aimed at limiting access solely to medical use, came into force on 16 August 1976.

It is essential to note that while THC was scheduled by both the US legislation and the superseding treaty of 1971/1976, CBD was never scheduled in either codification and thus remains outside both the Controlled Substances Act of 1970 and the Conventions of 1961 and 1971. As of 2013, 183 States [i.e., countries] are signatories to this Convention leaving CBD legal in all of them, despite popular misconceptions to the contrary.

When in private legal practice one of the authors (Ralph Fucetola JD) handled the DHEA Cases in 1994. He represented several people illegally arrested for possession of DHEA, which was, and is, lawful to possess as a normal bodily substance and nutrient. These cases, fought on behalf of the Life Extension Foundation, stand for the proposition that substances cannot be proscribed without clear legal authority (the presumption must be that a nutrient is lawful).[7] Similarly CBD, endogenous to the human body may not be proscribed.

Further, it is important to note that the growing of, and trade in, industrial hemp is explicitly permitted by international treaty:

[4] Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Schedule I drugs are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence. Some examples of Schedule I drugs are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote http://www.dea.gov/druginfo/ds.shtml

[5] http://www.unodc.org/unodc/en/treaties/single-convention.html

[6] http://www.unodc.org/pdf/convention_1971_en.pdf

[7] http://www.lifespirit.org/dhealegal.html

"This Convention shall not apply to the cultivation of the cannabis plant exclusively for industrial purposes (fiber and seed) or horticultural purposes."[8]

It is therefore our conclusion that CBD, a normal constituent of our bodies, not listed in any contraband statute, and not an "intoxicant", remains lawful to produce, buy, sell, possess and use under the Common Law.

Since CBD was available as a nutrient (a constituent of nutrient hemp seeds) prior to the grandfathering date of the Dietary Supplement Health and Education Act of 1994 (DSHEA) it therefore remains a DSHEA-protected nutrient.

Under the Common Law of the American States, statutes in derogation of the Common Law must be explicit and are to be strictly construed. Such strict construction precludes extending what is left of the Marijuana Prohibition to CBD.

Section 2: Cannabinoids Inside and Outside the Body

Cannabis, whether marijuana (high THC, low to moderate levels of CBD) or Industrial Hemp (high CBD, low to very low levels of THC) contains over 100 biologically active compounds[9] of which Delta-9-tetrahydrocannabinol (THC) is considered the most psychoactive.[10]

It is important to note that much of the debate about whether THC has a place in medicine has actually long been moot since *synthetic* THC has been available in the United States for *medical* use as Dronabinol (Marinol™), a Schedule III substance, and Nabilon (Cesamet™) , a Schedule II substance. Dronabinol was approved in 1986 for patient use and Nabilone was approved in the US in 1985 but only marketed in the US from 2006 onward.[11]

Thus, patients and doctors have had the opportunity to experience, gain wisdom and learn about THC for medical purposes for nearly 30 years.

Dranabinol has a daunting array of side effects including drowsiness, unsteady gait, dizziness, inability to focus, confusion, mood changes, delusions, and hallucinations leading to poor toleration.[12]

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[8] United Nations Single Convention on Narcotic Drugs, 1961, 1972, Article 28.

[9] Mehmedic Z, Chandra S, Slade D, et al. Potency trends of ?9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci. 2010;55:1209-1217.

[10] Ashton H. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry. 2001;178:101-106.

[11] http://en.wikipedia.org/wiki/Nabilone

[12] http://www.webmd.com/drugs/drug-9308Marinol+Oral.aspx?drugid=9308&drugname=Marinol+Oral&pagenumber=6

A recent placebo controlled, randomized, double blind study showed that these effects were similar to smoked high THC cannabis (marijuana) making it highly problematic for people with chronic pain.[13] The side effect profile for Nabilone is similar, leading to its lack of success as a medical alternative.[14],[15]

It is our belief that although the number of papers, information on, attention to and investment in THC has grown rapidly in recent years, THC is not the most important medical cannabinoid. That honor goes, we believe, to CBD, Cannabadiol.

In addition to its production in high proportion in selected cultivars of the Cannabis species, CBD is, importantly, produced by the human (and other mammalian) body.

In their 2014 review, Husni, et. al, stated, "Targeting the cannabinoid receptors has the potential [for] …a variety of conditions such as pain, neurodegeneration, appetite, immune function, anxiety, cancer, and others."[16]

Even a casual review of the science behind that statement makes it clear that, glowing as it is, it is far too limited in scope.

The Endocannabinoid System (ECS) is a group of neuromodulatory lipids and their receptors in the brain, peripheral nervous system[17],[18],[19] and elsewhere[20],[21] which are central to normal structure and function in a number of physiological processes including:

- Appetite[22],[23],[24],[25],[26]

[13] Issa MA, Narang S, Jamison RN, et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain. 2014;30:472-478.
[14] rWesnes KA, Annas P, Edgar C, et al. Nabilone produces marked impairments to cognitive function and changes in subjective state in healthy volunteers. J Psychopharmacol. 2010;24:1659-1669.
[15] Russo EB. The solution to the medical cannabis problem. In: Schatman ME, ed. Ethical Issues in Chronic Pain Management. New York: Informa Healthcare; 2007:165-194.
[16] http://www.ncbi.nlm.nih.gov/pubmed/25419092
[17] Fortin D, Levine E (2007). "Differential effects of endocannabinoids on glutamatergic and GABAergic inputs to layer 5 pyramidal neurons". *Cereb. Cortex* **17** (1): 163–74.
[18] Good C (2007). "Endocannabinoid-dependent regulation of feedforward inhibition in cerebellar Purkinje cells". *J. Neurosci.* **27** (1): 1-3
[19] Hashimotodani Y, Ohno-Shosaku T, Kano M (2007). "Presynaptic monoacylglycerol lipase activity determines basal endocannabinoid tone and terminates retrograde endocannabinoid signaling in the hippocampus". *J. Neurosci.* **27** (5): 1211–9.

[20] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2219532/
[21] http://onlinelibrary.wiley.com/doi/10.1111/bph.13050/abstract
[22] Elphick M, Egertová M (March 2001). "The neurobiology and evolution of cannabinoid signalling". *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* **356** (1407): 381–408. (April 2001). "Leptin-regulated endocannabinoids are involved in maintaining food intake". *Nature* **410** (6830): 822–5.

- Energy Balance and Metabolism, Including Insulin Sensitivity[27]
- Motor Learning[28]
- Pain sensation[29],[30],[31],[32]
- Synaptic plasticity[33]
- Mood[34],[35],[36]
    - Moodiness
    - Anxiolytic[37]
    - Stress Response[38],[39],[40]
    - Post Traumatic Stress Response

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[23] Kirkham T, Tucci S (2006). "Endocannabinoids in appetite control and the treatment of obesity". *CNS Neurol Disord Drug Targets* **5** (3): 272–92.
[24] Di Marzo V, Goparaju S, Wang L, Liu J, Bátkai S, Járai Z et al. (April 2001). "Leptin-regulated endocannabinoids are involved in maintaining food intake". *Nature* **410** (6830): 822–5.
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[34] http://www.ncbi.nlm.nih.gov/pubmed/19839936
[35] www.ncbi.nlm.nih.gov/pubmed/23261685
[36] http://www.biolmoodanxietydisord.com/content/3/1/19
[37] Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology. 1982;76:245-250.
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[39] *Campos AC, Ferreira FR, Guimarães FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. J Psychiatr Res. 2012 Nov;46(11):1501-10.*
[40] *Fusar-Poli P, Crippa JA, Bhattacharyya S, et al. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. 2009 Jan;66(1):95-105.*

- Memory[41]
- Immune functioning[42],[43],[44]
- Addiction[45]
- Neuromodulators for memory[46] and a wide variety of other processes[47]
- Autonomic Regulation[48]
- Sleep Regulation[49],[50],[51],[52]
- Thermoregulation[53],[54],[55]
- Female Reproduction through the early expression of fetal Endocannabinoid receptors responding to endocannabinoids expressed by the uterus[56],[57],[58]

[41] www.ncbi.nlm.nih.gov/pubmed/21104385
[42] Pertwee R (April 2006). "The pharmacology of cannabinoid receptors and their ligands: an overview". *Int J Obes (Lond)* **30** (Suppl 1): S13–8.
[43] Basu S, Ray A, Dittel B (December 2011). "Cannabinoid receptor 2 is critical for the homing and retention of marginal zone B lineage cells and for efficient T-independent immune responses". *J. Immunol.* **187** (11): 5720–32
[44] Pertwee R (January 2008). "The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin". *Br. J. Pharmacol.* **153** (2): 199–215.
[45] B.S. Basavarajappa, B.L. Hungund. Neuromodulatory role of the endocannabinoid signaling system in alcoholism: an overview, February 2002Volume 66, Issues 2-3, Pages 287–299

[46] http://www.ncbi.nlm.nih.gov/pubmed/16751707
[47] Ibid
[48] Elphick M, Egertová M (March 2001. Op Cit
[49] Murillo-Rodríguez E, Sánchez-Alavez M, Navarro L, Martínez-González D, Drucker-Colín R, Prospéro-García O (November 1998). "Anandamide modulates sleep and memory in rats". *Brain Res.* **812** (1–2): 270–4.
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[55] Pertwee R (April 2006). Op Cit
[56] Maccarrone M, Valensise H, Bari M, Lazzarin N, Romanini C, Finazzi-Agrò A (2000). "Relation between decreased anandamide hydrolase concentrations in human lymphocytes and miscarriage". *Lancet* **355** (9212): 1326–9.

- Mitigation of psychoactive substances including alcohol[59] and THC[60].[61]

How Safe is THC?

Can the same be said for THC, the current darling of the medical herb world?

However popular it may be, popularity cannot mitigate the potential toxicity of a substance. Chemical species like THC may cause hippocampal volume reduction (e.g., shrinking). Endocannabinoids as well as exogenous CBD *reduces* this effect in chronic THC uses, as has been known since the 1970's.[62].[63]

While hippocampal shrinkage has been associated with the development of psychosis, including that induced by the use of high THC/low CBD marijuana[64], we now understand more about the role of CBD in neuroprotection against this type of psychosis.[65].[66],[67],[68]

Cannabinoid receptors are currently identified as CB1, mainly expressed in the nervous systems and CB2, mainly expressed in the immune system.

However, consistent with the multiple clinical benefits found with CBD, an important series of recent studies have shown that endocannabinoids are expressed beyond the distribution of the known cannabinoid receptors in the brain, which suggests that these molecules may also be interacting with other receptors and involved with other cell processes.[69]

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[57] Das S, Paria B, Chakraborty I, Dey S (1995). "Cannabinoid ligand-receptor signaling in the mouse uterus". *Proc. Natl. Acad. Sci. U.S.A.* **92** (10): 4332–6.
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[59] B.S. Basavarajappa, op. cit.
[60] http://www.cell.com/trends/neurosciences/abstract/S0166-2236%2898%2901283-1
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[69] Elphick M, Egertová M (March 2001). Ibid

We also know that they are expressed in other locations as well, that CB1 is found in immune tissues just as CB2 can be found in the nervous system and that the tissues themselves secrete, on an as needed basis, substances which are agonistic to CB1 and CB2 receptors.

It is no wonder, then, that CBD is central to homeostasis, to healthy regulation and function of normal structure and function of so many diverse functions in the body.

While the ECS is clearly vital to normal structure and function of a wide variety of tissues and functions and CBD has an enviable safety profile, what about THC?

Lamentably, the picture is far less rosy in terms of toxicity and adverse consequences of administration for THC.

- THC is an important endocrine disruptor, an impact has been long known. In 2014 its estrogen disruption functions were characterized and documented. They were shown to be based on a more profound and impactful mechanism of disrupting cell signaling rather than by binding to estrogen receptors[70] as previously thought.
- Smoking high THC hemp is often compared to tobacco smoking in order to characterize the dangers of combusted and inhaled THC.

Both cigarette and THC use impair the sense of smell. 20 mg of THC delivered orally impaired the olfactory functions of all test subjects.[71]

In terms of the actual compounds burned and inhaled, the comparison may be somewhat apt. It is true that both tobacco and cannabis each have about 4000 compounds which are known so far and that most of these chemicals are, essentially, identical.[72] However, given the ever-shifting THC/CBD ratios of smoked or inhaled marijuana or hemp, the comparison becomes more difficult to make, especially considering that few people smoke as much cannabis as tobacco and a great many cannabis smokers are also tobacco users.[73]

With respect to other health consequences to THC use, however, the picture is less foggy. The American Academy of Neurology did an extensive review of the cardiopulmonary risks associated with heavy high THC smoked or "vaped" (vaporized and inhaled) marijuana

[70] http://www.ncbi.nlm.nih.gov/pubmed/25177025
[71] http://www.ncbi.nlm.nih.gov/pubmed/24802974
[72] Henry JA, Oldfield WL, Kon OM. Comparing cannabis with tobacco. BMJ. 2003;326:942-943.
[73] Ibid

concluding "smoking and possibly even use of vaporized [marijuana] preparations expose users to carbon monoxide and other respiratory toxins."[74]

Examining the cardiovascular, cerebrovascular, and peripheral vascular effects of smoked marijuana, another recent review showed that there is a deeply worrying direct correlation between smoked/inhaled/vaped high THC hemp (that is, marijuana) and acute myocardial infarction and increased cardiovascular mortality.[75]

Another extensive review was not able to conclusively establish a connection between THC inhalation and lung cancer, but the review was able to definitively conclude that it is associated with chronic bronchitis because of the association between smoked/inhaled THC marijuana and inflammation of large airways, increased airway resistance, and lung hyperinflation, all of which are consistent with the development of chronic bronchitis.[76]

The conclusion of yet another review on smoking high THC cannabis was quite clear: "smoking of cannabis is not medically recommended due to the potential respiratory tract dangers of noxious compounds such as polycyclic aromatic hydrocarbons, tar and carbon monoxide."[77]

It is therefore undeniable that both pulmonary and cardiovascular health may be compromised by the smoking/vaping of high THC Cannabis.

The association between marijuana inhalation and higher rates of acute myocardial infarction and increased cardiovascular mortality is quite clear. The same study described published case reports that identify a "safety signal" between cannabis use and stroke.[78]

- Psychological consequences of THC use have been reported at least since 1944 when reports of negative psychological consequences of THC use noted that subjects given marijuana showed anxiety and dysphoria.[79]

- Addiction potential has been noted or some time. High THC Cannabis when used heavily can be quite unpleasant and difficult to cease using, for some users, especially suddenly. Experiences include:[80],[81],[82],[83],[84]

[74] Koppel BS, Brust JC, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82:1556-1563.
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- Irritability
- Nervousness
- Sleep difficulty
- Decreased appetite
- Restlessness
- Depressed mood
- Physical symptoms and discomfort

Although the exact mechanism is not precisely understood, the phenomenon of depersonalization in habitual THC users is well established[85] and may be due to long half-life of cannabis metabolites and residual THC-related neurotoxicity.[86]

- Apparently permanent neurodegenerative changes in chronic THC use have been well documented[87],[88]. Those areas richest in CB1 receptor expression are at most risk of volume reduction through heavy long-term use of THC.[89]

  Cerebral brain structure volumes are integral to proper functioning. Atrophy of any part of the brain at any time after the neo natal neuronal "die off" is of great concern and can in no way be considered normal. Several studies compared the hippocampus, amygdala, and cerebellum in adult and adolescent heavy users compared with healthy controls. The

[80] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5). Washington, DC: American Psychiatric Publishing; 2013.
[81] Levin KH, Copersino ML, Heishman SJ, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. Drug Alcohol Depend. 2010;111:120-127.
[82] Milin R, Manion I, Dare G, Walker S. Prospective assessment of cannabis withdrawal in adolescents with cannabis dependence: a pilot study. J Am Acad Child Adolesc Psychiatry. 2008;47:174-178.
[83] Copersino ML, Boyd SJ, Tashkin DP, et al. Cannabis withdrawal among non-treatment-seeking adult cannabis users. Am J Addict. 2006;15:8-14.
[84] Mennes CE, Ben Abdallah A, Cottler LB. The reliability of self-reported cannabis abuse, dependence and withdrawal symptoms: multisite study of differences between general population and treatment groups. Addict Behav. 2009;34:223-226.
[85] Moran C. Depersonalization and agoraphobia associated with marijuana use. Br J Med Psychol. 1986;59(Pt 2):187-196.
[86] Karila L, Roux P, Rolland B, et al. Acute and long-term effects of cannabis use: a review. Curr Pharm Des. 2014;20:4112-4118.
[87] http://www.ncbi.nlm.nih.gov/pubmed/18519827
[88] http://www.ncbi.nlm.nih.gov/pubmed/21050680
[89] http://www.nature.com/npp/journal/v39/n9/full/npp201467a.html

results were not positive for THC users. All of the studies found that heavy marijuana use resulted in smaller volumes of these critically important CB1-rich brain structures.[90]

There are a host of other health concerns associated with recreational and medical marijuana use.

Again, the authors emphasize that we endorse the right of everyone to make their own health and recreation choices but the risks and problems associated with THC use may neither be rare or trivial.

- Overall mortality risk increases with THC use. Many factors interact in overall mortality statistics in general and the mortality statistics for marijuana uses is no different. A major review looking at this topic established that overall mortality from fatal motor vehicle accidents, AIDS, and lung cancer was significantly higher in marijuana users than in controls[91]

There are a variety of well-established health hazards associated with regular (daily or more frequent) marijuana use including

- Progression of liver fibrosis in those with Hepatitis C[92]
- Cannabinoid Hyperemesis Syndrome (cyclic nausea, vomiting and compulsive bathing)[93] understood to be due to rising THC levels
- Conjunctivitis which is understood to be due to an allergic response to *Cannabis sativa*[94]
- Severe oral health impacts in THC smokers include
    - Uvulitis[95]
    - Nicotinic stomatitis[96]
- Male reproductive function disruption[97]

[90] Matochik JA, Eldreth DA, Cadet JL, Bolla KI. Altered brain tissue composition in heavy marijuana users. Drug Alcohol Depend. 2005;77:23-30.
[91] Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug Alcohol Rev. 2010;29:318-330.
[92] Hezode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatology. 2005;42:63-71.
[93] Chen J, McCarron RM. Cannabinoid hyperemesis syndrome: a result of chronic, heavy cannabis use. Current Psychiatry. 2013;12:48-54.
[94] Mayoral M, Calderón H, Cano R, Lombardero M. Allergic rhinoconjunctivitis caused by Cannabis sativa pollen. J Investig Allergol Clin Immunol. 2008;18:73-74.
[95] Rawal SY, Tatakis DN, Tipton DA. Periodontal and oral manifestations of marijuana use. J Tenn Dent Assoc. 2012;92:26-31.
[96] Rawal, SY, Ibid

- Female reproductive function disruption because long term and/or heavy use of THC has been shown to:
    - Disrupt the menstrual cycle, suppressing the development of oocytes (eggs)[98]
    - Disrupt successful implantation of embryos in the uterus[99]
    - Lead to fetal brain damage and impaired cognitive development[100],[101]
        - Inattention
        - Impulsivity
        - Impairment
            - Learning
            - Memory
        - Executive functioning
        - Reduction in birth weight[102]

Are there other, more positive health benefits of THC use which might outweigh the risks of its use??

What exactly are people smoking?

The content of marijuana has been genetically and otherwise altered over the last 20 years to substantially increase its THC content.[103] Natural, unaltered Cannabis contains a maximum of 10-15% THC[104] whereas dispensaries online now offer THC content as high as 33%.[105]

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[97] Barazani Y, Katz BF, Nagler HM, Stember DS. Lifestyle, environment, and male reproductive health. Urol Clin North Am. 2014;41:55-66.
[98] Mayoral M, Calderón H, Cano R, Lombardero M. Allergic rhinoconjunctivitis caused by Cannabis sativa pollen. J Investig Allergol Clin Immunol. 2008;18:73-74.
[99] Mayoral M, Ibid.

[100] Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol. 2011;6:459-480.

[101] Karila L, Cazas O, Danel T, Reynaud M. [Short- and long-term consequences of prenatal exposure to cannabis]. J Gynecol Obstet Biol Reprod (Paris). 2006;35:62-70.
[102] Gray TR, Eiden RD, Leonard KE, et al. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. Clin Chem. 2010;56:1442-1450.
[103] Henry JA, Op. Cit.

It is important to note that --

- Low concentrations of THC tend to reduce anxiety (e.g., are anxiolytic)[106]
- High concentrations of THC tend to produce anxiety (e.g., are anxiogenic)[107]
- While people with anxiety may gravitate toward high THC marijuana use, there is insufficient evidence to support the a connection that would support THC as a causal factor in anxiety.[108],[109]
- There is also insufficient evidence to link high THC marijuana use as a causal factor in bipolar disorder although marijuana use is associated with earlier onset of mania.[110]
- Long-term THC use increases
    - Major depression risk[111]
    - Vivid suicidal ideation[112]
    - Suicide attempt risk[113]

Early and prolonged marijuana use carries special risks. Frequent THC use by adolescents predicted depression and anxiety[114],[115] The variables and vagaries are enormous: in fact, "Medical Marijuana" THC content may, in fact, be higher than either legal or [p'p[illegal recreational marijuana.[116],[117]

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[104] Aggarwal SK, Pangarkar S, Carter GT, Tribuzio B, Miedema M, Kennedy DJ. Medical marijuana for failed back surgical syndrome: a viable option for pain control or an uncontrolled narcotic? PM R. 2014;6:363-372.
[105] Vermont Herbal Center. Weed menu. https://weedmaps.com/dispensaries/in/california/hollywood Accessed November 5, 2014.
[106] Moreira FA, Wotjak CT. Cannabinoids and anxiety. Curr Top Behav Neurosci. 2010;2:429-450.
[107] Ibid
[108] Crippa JA, Zuardi AW, Martin-Santos R, et al. Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol. 2009;24:515-523.
[109] Agrawal A, Lynskey MT. Cannabis controversies: how genetics can inform the study of comorbidity. Addiction. 2014;109:360-370.
[110] Bally N, Zullino D, Aubry JM. Cannabis use and first manic episode. J Affect Disord. 2014;165:103-108.
[111] Reece AS. Chronic toxicology of cannabis. Clin Toxicol (Phila). 2009;47:517-524.
[112] Price C, Hemmingsson T, Lewis G, Zammit S, Allebeck P. Cannabis and suicide: longitudinal study. Br J Psychiatry. 2009;195:492-497.
[113] Serafini G, Pompili M, Innamorati M, Rihmer Z, Sher L, Girardi P. Can cannabis increase the suicide risk in psychosis? A critical review. Curr Pharm Des. 2012;18:5165-5187.
[114] Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: cohort study. BMJ. 2002;325:1195-1198.
[115] Hadland SE, Harris SK. Youth marijuana use: state of the science for the practicing clinician. Curr Opin Pediatr. 2014;26:420-427.
[116] Burgdorf JR, Kilmer B, Pacula RL. Heterogeneity in the composition of marijuana seized in California. Drug Alcohol Depend. 2011;117:59-61.

While the causal relationship between marijuana, anxiety, bipolar and major depression is not clear, the literature is much less ambiguous about psychosis. Marijuana-related psychosis, which appears to be a relatively rare occurrence given the large number of recreational users, presents in a manner which is virtually indistinguishable from schizophrenia.[118],[119],[120],[121],[122]

It is important to note that any apparent psychotic state may not persist past the intoxication with marijuana leaving no evident effects[123] and this is, in fact, a large part of its wide appeal.

THC is widely known to impair perception, this, too, being part of its attraction. There is strong evidence to conclude that acute cognitive impairment takes place with heavy marijuana use in the areas of:[124]

- Attention
- Concentration
- Inhibition
- Impulsivity
- Working memory

The acute impairment is widely believed to be transient but a recent study of 1000 participants followed from birth to age 38 showed that for adolescent marijuana users, after they ceased using marijuana their function was never fully restored.[125]

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[117] Yucel M, Zalesky A, Takagi MJ, et al. White-matter abnormalities in adolescents with long-term inhalant and cannabis use: a diffusion magnetic resonance imaging study. J Psychiatry Neurosci. 2010;35:409-412.
[118] Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot—a review of the association between cannabis and psychosis. Front Psychiatry. 2014;5:54.
[119] van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol. 2002;156:319-327.
[120] Ferdinand RF, Sondeijker F, Van Der Ende J, Selten JP, Huizink A, Verhulst FC. Cannabis use predicts future psychotic symptoms, and vice versa. Addiction. 2005;100:612-618.
[121] McGrath J, Welham J, Scott J, et al. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry. 2010;67:440-447.
[122] Kuepper R, Van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. BMJ. 2011;342:d738.
[123] Radhakrishnan R, Addy PH, Sewell RA, et al. Cannabis, cannabinoids and the link with psychosis. In: Madras B, Kuhar M, eds. The Effects of Drug Abuse on the Human Nervous System. San Diego, Calif: Academic Press (Elsevier); 2014:423-474.
[124] Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med. 2011;5:1-8.
[125] Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012;109:E2657-E2664.

Some suggest widespread use of high THC Marijuana should lead adults (or their doctors) to be concerned with progressive and permanent cognitive damage whether its use is medical or recreational.[126]

Clearly, THC has a potential toxic profile, but is it medically useful or indicated? If it is indicated, under what circumstances?

As mentioned above, synthetic THC has been available for decades and is poorly tolerated.

What about natural THC?

Very low doses of THC may, along with other antioxidants and neuro protective molecules, slow the production and aggregation of beta amyloid in Alzheimer's disease and offer assistance to people with that condition by helping to slow its progression.[127]

Ultra-low doses (between 3-4 orders of magnitude lower than doses shown to cause psychoactive and physiological effects) of THC administered prior to, during and after, experimental drug-induced brain injury in animals was shown to be neuro-protective with protection lasting for up to 7 weeks after exposure to the ultra-low dose THC.[128]

Balancing this, however, another study showed that the same type of ultra-low dose THC administration caused long term deficits in cognitive functioning: "that lasted for at least 5 months. The behavioral deficits were detected by several tests that evaluated different aspects of memory and learning, including spatial navigation and spatial and non-spatial recognition. Our findings point to possible deficits in attention or motivation that represent a common upstream cognitive process that may affect the performance of the mice in the different behavioral assays. Similar ultra-low doses of THC (3-4 orders of magnitude lower than doses that are known to evoke the acute effects of THC) also induced sustained activation of extracellular-regulated kinase (ERK1/2) in the cerebellum, indicating that a single injection of such low doses of the cannabinoid drug can stimulate neuronal regulatory mechanisms."[129] Pointing to a need to evaluate findings carefully.

It is interesting to note that the above two studies were summarized in the popular literature to suggest that researchers found that THC "protected brain cells and preserved cognitive function over time" and suggested that it could be used preventively, for ongoing

[126] Solowij N, Yucel M, Lorenzetti V, Lubman D. Does cannabis cause lasting brain damage? In: Castle D, Murray RM, D'Souza DC, eds. Marijuana and Madness. Cambridge, UK: Cambridge University Press; 2012:103-113.
[127] Chuanhai Cao, Yaqiong Li, Hui Liu, Ge Bai, Jonathan May, Xiaoyang Lin, Kyle Sutherland, Neel Nabar and Jianfeng Cai; "The Potential Therapeutic Effects of THC on Alzheimer's Disease," *Journal of Alzheimer's Disease*, DOI: 10.3233/JAD-140093.
[128] http://www.ncbi.nlm.nih.gov/pubmed/22821081
[129] http://www.ncbi.nlm.nih.gov/pubmed/19766676

protection. "Studies done in 2012 [here, referenced as footnote 114 – the authors] and 2013 [here referenced as footnote 115 – the authors] found that a low dose of THC protected mice's brains from damage by carbon monoxide and head trauma."[130]

Upon actually reading the papers, neither paper justified any such glowing interpretation.

This kind of adoring misinterpretation, coupled with the poor data referenced above on dosing, etc., supports the following conclusions:

- Multiple systematic reviews of medical cannabis in which formulation, dosage, and route of administration were specified or were consistent across randomized controlled trials have failed to yield definitive conclusions regarding the safety and efficacy of medical cannabis for a variety of conditions.[131,132,133,134,135,136,137,138,139,140]
- Considering this ambiguity, how are providers supposed to know which cannabinoids, formulations, dosages, and routes of administration are safe, tolerable, and effective, and in which conditions and for which patients?

[130] http://www.alternet.org/drugs/pot-could-save-your-life-4-ways-cannabis-good-your-brain?akid=12796.108705.jCKxsv&rd=1&src=newsletter1031917&t=7

[131] Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. Br J Clin Pharm. 2011;72:735-744.

[132] Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ. 2001;323:13-16.

[133] Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001;323:16-21.

[134] Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl). 2008;17:431-443.

[135] Pittler MH, Ernst E. Complementary therapies for neuropathic and neuralgic pain: systematic review. Clin J Pain. 2008;24:731-733.

[136] Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009;10:1353-1368.

[137] Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. BMC Neurol. 2009;9:59.

[138] Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010;28;5:e14433.

[139] Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. Sleep Med Rev. 2014;18:477-487.

[140] Sznitman SR, Zolotov Y. Cannabis for therapeutic purposes and public health and safety: a systematic and critical review. Int J Drug Policy. 2015;26:20-29.

- Unfortunately, current arguments for the use of medical cannabis are considerably more politically, and often emotionally, based, than scientifically based, resulting in the proliferation of "medical marijuana pseudoscience."[141]

What is not pseudoscience is often just plain poor science. In a much-touted study determining that Traumatic Brain Injury (TBI) victims with THC in their blood had a major improvement in mortality from their injuries (80% increase in survival odds) compared to THC negative TBI victims[142], it is clear that while THC was screened for, CBD was not and thus we have no idea whether THC was, in fact, neuro-protective or whether CBD (or some other cannabinoid) provided the protection. Without that parallel information, although widely touted, the study provides little in the way of substance.

Based on the preponderance of evidence, a reasonable person, not financially or otherwise wedded to THC use, would have to conclude that the active protection might well have come from CBD present since its important endogenous functions in the body include anti-inflammatory ones, critically important in brain injury outcomes. This was not explored by the authors of the study and is never mentioned when the paper is sited by the pro THC press which reported, for example,

> "*This means that in a group of occasional pot smokers and a group of abstainers who suffer similar brain injuries, the pot smokers will have only 2 deaths for every 10 suffered by the abstainers! There are 52,000 deaths every year from TBI in America. This study showed that if every adult American had a puff of cannabis once a week, 80% of those deaths would be avoided – that's about 41,600 lives that could be saved, every year. Why isn't this front page news?*"[143]

The first medical marijuana law in the US, California's Compassionate Use Act of 1996, legislated that marijuana could be recommended to a patient by a physician for "treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, **or any other illness for which marijuana provides relief**."[144] [Emphasis added by the authors.]

The specific conditions and their general expansion to any other condition opened up the possibilities of a massive natural experiment in which people and their doctors had the legal (at least at the State level) opportunity to explore possibilities both consistent with

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[141] Schatman, Michael, Medical Marijuana: The State of the Science, http://www.medscape.com/viewarticle/839155_4

[142] http://www.ingentaconnect.com/search/article?option2=author&value2=plurad&pageSize=10&index=7

[143] http://www.alternet.org/drugs/pot-could-save-your-life-4-ways-cannabis-good-your-brain?akid=12796.108705.jCKxsv&rd=1&src=newsletter1031917&t=7 op. cit.

[144] California Department of Public Health. Proposition 215. http://www.cdph.ca.gov/programs/mmp/pages/compassionateuseact.aspx Accessed November 14, 2014.

those already explored in the literature and those not yet tested, creating a fertile field for the growth of both health freedom and health.

Medical marijuana laws in the US list "pain" as a suitable indication for registration as a medical marijuana use. A recent study of the indications for which people seek medical marijuana registration offers a provocative finding: 94% of all registered uses listed "severe pain" as their reason for seeking registration[145] suggesting that inadequate data are available as to why people actually seek and obtain medical marijuana registration.

Definition of what constitutes "medical marijuana" is lacking, as is data on satisfactory (or unsatisfactory) endpoint measures. We have little or no real data on whether the use of medical marijuana is causing a significant impairment of patient function, as we know happens in recreational use of High THC/Low CBD Cannabis. And what of the worrying brain, pulmonary, cardiovascular and mortality changes seen in recreational marijuana users?

We do not have adequate data to supply to would-be users, current users or past users although this data is critically important for those who wish to give informed consent, practitioners who need to be able to discuss these realities with patients.

This is not to say that for difficult to treat and intractable conditions, a trial of medical marijuana is not justified. But although marijuana is used for medical purposes, its use is episodic, idiosyncratic, empirical and absolutely not scientific for the reasons mentioned above.

High THC/Low CBD preparations are easily available in dispensaries in states where legal while Low THC/High CBD preparations are virtually unobtainable making the same kind of natural experiment as the one that is taking place with High THC/Low CBD impossible.

Studies looking at pain relief of THC/CBD combinations and THC alone (e.g., in oralmucosal spray form) concluded that the spray form was effective and well tolerated[146]. But, interestingly, while THC was evaluated alone, CBD was not, adding, once again, to THC pseudoscience).

What About Cancer? THC, CBD or Both?

Perhaps the most contentious area of THC use is in cancer treatment. It may, in fact, have a vigorous and important role to play in this area but even saying so is ringed with prohibitions and pitfalls. As an herb, it is illegal under US Statute[147] to use the words

[145] Kondrad E, Reid A. Colorado family physicians' attitudes toward medical marijuana. J Am Board Fam Med. 2013:26:52-60.
[146] http://www.ncbi.nlm.nih.gov/pubmed/23141881
[147] Dietary Supplements Health and Education Act, 1994

"treatment", "cure", "diagnosis" or "prevent" ("mitigate" was later added as a proscribed word by the FDA).

Therefore, this discussion will eschew the terms listed above and speak only about "restoring normal structure and function" in living creatures (*in vivo*) and actions seen in the laboratory studies (*in vitro*). The reader is left to interpolate the forbidden words mentally.

In 2007, *in vitro* studies by McAlister, et. al., showed that aggressive tumors with high levels of the id-1 gene (associated with metastasis) exposed to CBD showed inhibited expression of that gene, also inhibiting metastasis of the tumor. "…cannabidiol (CBD), a cannabinoid with a low-toxicity profile, could down-regulate Id-1 expression in aggressive human breast cancer cells. The CBD concentrations effective at inhibiting Id-1 expression correlated with those used to inhibit the proliferative and invasive phenotype of breast cancer cells. CBD was able to inhibit Id-1 expression at the mRNA and protein level in a concentration-dependent fashion."[148] The authors went on to note, "CBD represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumor aggressiveness."[149]

Numerous other studies show clearly that CBD and related compounds, absent THC, support the eliminating of cancer cells *in vitro* and *in vivo*. For example, W. Liu in a study funded by GW Pharmaceuticals, which already makes a drug for MS patients made from CBD, found that cannabinoids, including CBD, were effective in bringing about a dramatic reduction in leukemia cell viability [150]

Famously, Rick Simpson wrote, taught and practiced[151] that THC, home-extracted, smoked or ingested, was effective in the treatment of many different diseases, including cancer. His widely viewed "Phoenix Tears" website and video are held forth as dogma by the THC faithful. But what does the science tell us about the deeply held belief in cancer treatment with THC?

Some preliminary studies suggest a role for THC in combination with CBD. For example, a combination of THC and CBD was found to have a dramatic impact on an animal model for glioma in combination with radiation treatment, *The Combination of Cannabidiol and Δ9-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model.* [152] This study has been widely cited in the popular press as justification for the joint use of THC and CBD in gliomas, which are generalized in the popular press as

[148] http://www.ncbi.nlm.nih.gov/pubmed/18025276
[149] Ibid
[150] http://ar.iiarjournals.org/content/33/10/4373.abstract#corresp-1
[151] http://phoenixtears.ca/

"brain tumors" although different brain tumors are biologically very different and respond very differently to treatments.

What the article's abstract, and the article itself, actually says is quite different since it shows that all forms of cannabinoids, including, but not limited to THC and CBD, increase the **radiation sensitivity of mouse glioma cells** (an animal model for glioblastoma in humans). *The article says that all combinations of cannabis components were more effective than any component alone. What it does NOT say is that THC and CBD are supra additive and more effective together than either alone in human brain cancers.*[153]

Is there, however, scientific documentation to support the widespread belief and contention that THC is

1. Curative alone in cancers

2. Supra additive with CBD so that the cancer treatment capacity of CBD is significantly enhanced by their joint use in in gliomas and other human brain tumors, or tumors in general without the use of radiation?

A widely cited and touted paper called "*Combining Components of Marijuana Enhances Inhibitory Effects on Brain Cancer*" was published by the California Pacific Medical Center, as memorialized in a press release from that institution.[154] The study was funded by NIH.

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[153] **Abstract: The Combination of Cannabidiol and Δ⁹-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model**

High-grade glioma is one of the most aggressive cancers in adult humans and long-term survival rates are very low as standard treatments for glioma remain largely unsuccessful. Cannabinoids have been shown to specifically inhibit glioma growth as well as neutralize oncogenic processes such as angiogenesis. In an attempt to improve treatment outcome, we have investigated the effect of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) both alone and in combination with radiotherapy in a number of glioma cell lines (T98G, U87MG, and GL261). Cannabinoids were used in two forms, pure (P) and as a botanical drug substance (BDS). Results demonstrated a duration- and dose-dependent reduction in cell viability with each cannabinoid and suggested that THC-BDS was more efficacious than THC-P, whereas, conversely, CBD-P was more efficacious than CBD-BDS. Median effect analysis revealed all combinations to be hyperadditive [T98G 48-hour combination index (CI) at FU_{50}, 0.77–1.09]. Similarly, pretreating cells with THC-P and CBD-P together for 4 hours before irradiation increased their radiosensitivity when compared with pretreating with either of the cannabinoids individually. The increase in radiosensitivity was associated with an increase in markers of autophagy and apoptosis. These in vitro *results were recapitulated in an orthotopic murine model for glioma, which showed dramatic reductions in tumor volumes when both cannabinoids were used with irradiation (day 21: 5.5 ± 2.2 mm^3 vs. 48.7 ± 24.9 mm^3 in the control group;* P < *0.01). Taken together, our data highlight the possibility that these cannabinoids can prime glioma cells to respond better to ionizing radiation, and suggest a potential clinical benefit for glioma patients by using these two treatment modalities. Mol Cancer Ther; 13(12); 2955–67. ©2014 AACR.*

[154] http://www.cpmc.org/about/press/news2010/thc-cbd-study.html

The article suggests that the widely sung glioma-treating effects of THC are enhanced by the addition of CBD while stating that the effects of the combination were not seen with either THC or CBD alone.[155]

The same journal published an article showing that implanted glioblastomas which were sensitive to, and which were resistant to, Temozolimide, a chemotherapeutic agent, were better treated with a combination of "submaximal doses" of THC/CBD.[156]

Several studies show a combinatorial effect through which cells are sensitized to the chemotherapeutic agent with the addition of a small amount of THC in leukemia[157], melanoma[158].

But looking beyond these studies we see the recent review of the literature by Fowler which concludes that while THC may turn out to have useful properties that has not yet been established while the evidence for such treatment use with CBD is already clear.[159]

While the common wisdom says that THC is a robust "treatment" molecule for cancer, the strength of that belief is questionable. There are cancer types, for example, MCF-7 breast cancer cells, which are, in vitro **induced to become cancerous by THC**. These are estrogen dependent cancer cells so the estrogen disruption mentioned above is of enormous significance here. Clearly, more knowledge is needed before we rush to judgment on THC use in cancer.[160]

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[155] **Abstract: Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival.** *The cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) receptor agonist Δ^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 Δ^9-THC. There are conflicting reports, however, as to what extent other cannabinoids can modulate Δ^9-THC activity, and most importantly, it is not clear whether other cannabinoid compounds can either potentiate or inhibit the actions of Δ^9-THC. We therefore tested cannabidiol, the second most abundant plant-derived cannabinoid, in combination with Δ^9-THC. In the U251 and SF126 glioblastoma cell lines, Δ^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 Δ^9-THC may improve the overall effectiveness of Δ^9-THC in the treatment of glioblastoma in cancer patients*. Mol Cancer Ther; 9(1); 180–9

[156] Torres, s., A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma et. al*Mol Cancer Ther; 10(1); 90–103. ©2011 AACR*.

[157] http://www.ncbi.nlm.nih.gov/pubmed/18608861

[158] http://www.ncbi.nlm.nih.gov/pubmed/25674907

[159] http://www.ncbi.nlm.nih.gov/pubmed/25669486

[160] http://www.ncbi.nlm.nih.gov/pubmed/?term=%CE%949-Tetrahydrocannabinol+%2B+cancer

How Safe IS CBD?

First isolated in 1934, CBD was partially synthesized from hashish in 1964 but not fully synthesized for several more years. It was viewed as an "irrelevant compound" for many years.[161],[162], Moreover, since it was determined that CBD *mitigated* the psychoactive effects of THC[163], it was deemed a problem to be eliminated and vigorous genetic engineering efforts[164] by illicit growers were employed to reduce the CBD content in cannabis plants while increasing the THC content sharply.[165] For these reasons, little was published about CBD or about its therapeutic value until 2000 when A.W. Zuardi wrote about CBD "with the confirmation of a plethora of pharmacological effects, many of them with therapeutic potential."[166]

The consensus among scholars and practitioners dealing with the topic at this point is stated well by Schatman writing in a recent (Feb 6, 2015) paper, "CBD is safer and more uniform in its composition than "medical marijuana," and it is associated with less variability in response to it, thereby giving it greater clinical value." [167]

Another recent major review has found conclusive evidence that the adverse psychological events associated with cannabis are caused by THC and mitigated by CBD.[168]

In contrast to the neurodegenerative changes brought about by heavy and long-term use of THC, it now emerges from a variety of sources that CBD actually induces the production of new cells (neurogenesis) in the brain[169],[170],[171] a profound and very important finding which stands in stark contrast to the brain volume reduction following THC use. Since we all have heavy and long-term use of CBD through its endogenous production and utilization, this is hopeful news, indeed.

The data show that not only are adult cells produced and stimulated to reproduce and function, but progenitor or "stem cells" are stimulated to reproduce and function as well. This is a clear indication not only of reparative capacity, but of regenerative (anti-aging) capacity since a

[161] Robson P. Therapeutic aspects of cannabis and cannabinoids. Br J Psychiatry. 2001;178:107-115.
[162] Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86:1646-1647.
[163] Wilkinson ST, D'Souza DC. Problems with the medicalization of marijuana. JAMA. 2014;311:2377-2378.
[164] Wilkinson ST, Ibid
[165] Burgdorf JR, Kilmer B, Pacula RL. Heterogeneity in the composition of marijuana seized in California. Drug Alcohol Depend. 2011;117:59-61.
[166] Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr. 2008;30:271-280.
[167] http://www.medscape.com/viewarticle/839155?src=wnl_edit_specol&uac=117629CN
[168] Niesink RJ, van Laar MW. Does cannabidiol protect against adverse psychological effects of THC? Front Psychiatry. 2013;4:130.
[169] http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8930251
[170] http://www.sciencedaily.com/releases/2005/10/051016083817.htm
[171] http://www.sciencedirect.com/science/article/pii/S0197018613002106

hallmark of young bodies is an abundance of stem cells while a hallmark of old ones is their paucity.

When cells in the hippocampus and subventricular centers die off and volume is reduced, clinical consequences can be identified as depression, anxiety, psychoses and senile dementias of various types and other serious and heretofore "irreversible" conditions and disorders.

Massi et. al. state, "the clinical use of Δ(9)-THC and additional cannabinoid agonists is often limited by their unwanted psychoactive side effects, and for this reason interest in non-psychoactive cannabinoid compounds with structural affinity for Δ(9)-THC, such as cannabidiol (CBD), has substantially increased in recent years. "[172]

With clear evidence for CBD-related neurogenesis of progenitor and adult cells, the picture changes not only clinically, but neurologically.

CBD, unlike THC, has a remarkable safety profile. In fact, in 1978, when the first study of CBD safety on humans was conducted by Mechoulam and Carlini the authors reported that they were not able to discern any toxic effects in epilepsy patients receiving the substance for 3 months[173]

The safety profile of CBD was further studied when patients with and without epilepsy received up to 300 mg of CBD per day. No aberrations in any parameters were found.[174] A 1991 study showed that while the symptoms and progression of Huntington 's Disease were not impacted by high dose CBD for 6 weeks, there were no statistically significant changes in any parameter studied.[175]

Additional studies looking at short term (5 week) administration for treatment resistant Schizophrenia[176] and up to 1200 mg CBD per day for bi-polar patients[177] similarly explicitly stated that there were no safety concerns in any participants of the study.

In a brief (3-week) study in which participants received 10 mg of oral CBD daily no changes in any parameter was found. The parameters examined included

- Neurologic evaluation including EEG studies

[172] http://www.ncbi.nlm.nih.gov/pubmed/22506672
[173] Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften. 1978;65:174-179.
[174] Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology. 1980;21:175-185.
[175] Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav. 1991;40:701-708.
[176] Zuardi AW, Hallak JE, Dursun SM, et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol. 2006;20:683-686.
[177] Zuardi AW, Crippa J, Dursun S, et al. Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol. 2010;24:135-137.

- Cardiac evaluation including ECG
- Psychiatric evaluation
- Clinical evaluation including blood chemistry and urinalysis.[178]

In a 4 week study of Parkinson's Disease patients receiving 400 mg per day of CBD, a similar lack of disturbances in physiology was found and neither cognitive nor negative motor changes were observed.[179]

In a trial in which CBD was administered orally, by inhalation or intravenously, there were no toxic changes or indications[180] although a recent systematic review suggested that sedation may occur at very high doses of CBD.[181]

A theoretical concern has been raised that while lower doses of CBD may stimulate immune function, high doses may result in immune suppression although this effect has not been seen in studies searching for them.[182]

Thus, other than a theoretical concern that immune suppression may occur in some sensitive patients and observed sedation at very high levels of administration, CBD's side effect and toxicity profile is more than admirable.

From general principles of nutrition, applied to what we know about CBD as a nutrient in the body, the authors conclude the primary health benefits of hemp are found in the CBD. Since CBD, as a dietary supplement, is a nutrient and constituent of food, it, like other foods, is deemed to be safe when used as directed.[183]

Section 3: Why and When Do We Need CBD?

[178] Mincis M, Pfeferman A, Guimaraes RX, et al. [Chronic administration of cannabidiol in man. Pilot study]. AMB Rev Assoc Med Bras. 1973;19:185-190.
[179] Zuardi A W, Crippa J, Hallak J, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol. 2009;23:979-983.
[180] Zuardi AW, Guimarães FS. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, ed. Cannabis in Medical Practice. Jefferson, NC: McFarland & Company, Inc.; 1997:133-141.
[181] Zhornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. Pharmaceuticals (Basel). 2012;5:529-552.
[182] Zuardi AW, Guimaraes FS, Moreira AC. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. Brazilian J Med Biol Res. 1993;26:213-217.
[183] http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/default.htm#responsible

It is the authors' contention that, despite the fervor which accompanies the debate, CBD is, in fact, safer, more effective, far better tolerated and thus, a much better choice for health-related purposes than THC. It is, of course, a poor choice for recreational use since its mood and other enhancements are totally non-psychoactive and therefore not very amusing.

CBD and Cancer: As Good As, Better, or Worse than THC or THC/CBD?

The support for CBD as a nutrient when dealing with cancer, in the absence of THC, is abundant. A small sample of the large amount of scientific literature available makes the point best: "As CBD is a non-psychoactive phytocannabinoid that appears to be devoid of side effects, our results support its exploitation… in the management of gliomas."[184] Some of these notes use medical terminology, which is unfortunate, as we intend to communicate only about CBD as a nutrient in order to comply with legislative and regulatory restrictions. We offer this information as fair comment to provide full disclosure, without adopting any language that might suggest that CBD is anything other than a nutrient with nutritional benefits. But, frankly, that's all you our your patients ever really need to achieve and maintain healthy status.

Moreover,

- "CBD can be used as a novel therapeutic option to inhibit growth and metastasis of highly aggressive breast cancer subtypes including TNBC, which currently have limited therapeutic options and are associated with poor prognosis and low survival rates"[185].
- Anti -invasive, anti-metastatic and multiple cancer cell killing mechanisms of CBD on lung cancer.[186]
- CBD "reduced proliferation and induced apoptosis in those infected by the [Kaposi sarcoma] virus."[187]
- CBD has an inhibitory effect on systemic malignant tumors.[188]
- "CBDA (the parent compound from which CBD is decarboxylated) possesses an anti-migrative potential for highly invasive cancer cells…. CBD [is] both an important experimental tool and as a lead compound for pharmaceutical development."[189]
- Lung cancer inhibited through action of CBD[190]

[184] http://www.ncbi.nlm.nih.gov/pubmed/24204703
[185] http://www.ncbi.nlm.nih.gov/pubmed/25660577
[186] http://www.ncbi.nlm.nih.gov/pubmed/25069049
[187] http://www.ncbi.nlm.nih.gov/pubmed/23264851
[188] http://www.ncbi.nlm.nih.gov/pubmed/23544909
[189] http://www.ncbi.nlm.nih.gov/pubmed/24088353
[190] http://www.ncbi.nlm.nih.gov/pubmed/24976505

- "Plant derived cannabinoids, especially cannabidiol, are potent inhibitors of prostate carcinoma viability in vitro. They also showed that the extract was active in vivo."[191]

- "CBD reduced breast cancer metastasis in advanced stages of the disease as the direct result of down-regulating the transcriptional regulator Id1."[192]

- "CBD reduced cell proliferation in tumoral, but not in healthy, cells. CBD attenuates colon carcinogenesis and inhibits colorectal cancer cell proliferation via CB1 and CB2 receptor activation."[193]

- "Cannabidiol (CBD) is a non-psychoactive plant cannabinoid that inhibits cell proliferation and induces cell death of cancer cells and activated immune cells."[194]

What else does CBD do safely, elegantly, cost effectively and efficiently? Pretty much everything that can be fixed through upregulation of immunity, down regulation of pain, inflammation, cell protection from toxic inputs, regulation of mood and neurologic function.

- "[C]annabidiol protects mouse liver from acute alcohol-induced steatosis through multiple mechanisms including attenuation of oxidative stress"[195]

- "CBDA is a selective cyclooxygenase-2 (COX-2) inhibitor [making it far safer than COX-2 inhibitors – REL][196]

- "CBD protects the Cardiovascular System "[197]

- Virtually every aspect of diabetic pathology is responsive to CBD.[198]

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[191] http://www.ncbi.nlm.nih.gov/pubmed/22849856
[192] http://www.ncbi.nlm.nih.gov/pubmed/24910342
[193] http://www.ncbi.nlm.nih.gov/pubmed/24373545
[194] http://www.ncbi.nlm.nih.gov/pubmed/24309936
[195] www.ncbi.nlm.nih.gov/pubmed/24398069
[196] http://www.ncbi.nlm.nih.gov/pubmed/24088353 loc. Sit.
[197] "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." http://www.ncbi.nlm.nih.gov/pubmed/22670794
[198] Abstract: "Oxidative stress and inflammation play critical roles in the development of diabetes and its complications. Recent studies provided compelling evidence that the newly discovered lipid signaling system (ie,

- "Our data strengthen our previous assumption that CBD, known to be safe in man, can possibly be used as a therapeutic agent in Type 1 diabetes."[199]

- Etc.

CBD, a natural constituent of the body may either be under produced or, if present in sufficient quantity, may be poorly utilized. Therefore repletion of this non-toxic endogenous substance makes perfect sense for enhancing regulation of normal structure and function in any area where its functions have been observed.

Section 4: Conclusion

CBD, produced by the Industrial Hemp plant, is both legal and useful. CBD has a strong place in the therapy of regulation of established difficulties and in the restoration of optimal function for long term health.

Unlike "Marijuana", CBD, with which many people around the world confuse it, has no significant concentration of intoxicant substance like THC which is currently banned in some jurisdictions. "Industrial Hemp" refers to a group of related cultivars which are rich in nutrient components that are collectively referred to as CBDs (cannabidiols) and very low (less than 0.3%) in psychoactive THC. Explorations of the use of CBD for recovery and repair can and should proceed on both the empirical and the organized levels.

Since CBD is non-toxic, assuming high purity in manufacture, there is no downside to its use in both doctor-mediated and home remedy situations.

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the endocannabinoid system) may significantly influence reactive oxygen species production, inflammation, and subsequent tissue injury, in addition to its well-known metabolic effects and functions. The modulation of the activity of this system holds tremendous therapeutic potential in a wide range of diseases, ranging from cancer, pain, neurodegenerative, and cardiovascular diseases to obesity and metabolic syndrome, diabetes, and diabetic complications. This review focuses on the role of the endocannabinoid system in primary diabetes and its effects on various diabetic complications, such as diabetic cardiovascular dysfunction, nephropathy, retinopathy, and neuropathy, particularly highlighting the mechanisms beyond the metabolic consequences of the activation of the endocannabinoid system. The therapeutic potential of targeting the endocannabinoid system and certain plant-derived cannabinoids, such as cannabidiol and Δ9-tetrahydrocannabivarin, which are devoid of psychotropic effects and possess potent anti-inflammatory and/or antioxidant properties, in diabetes and diabetic complications is also discussed. "http://www.ncbi.nlm.nih.gov/pubmed/22155112

[199] http://www.ncbi.nlm.nih.gov/pubmed/17714746

are involved with the cultivation of certified Organic, Low Radiation CBD. For more information, contact Ralph Fucetola, JD, Ralph@FundforNaturalSolutions.com .

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