

Medical Cannabis Research and Information

Compiled by Lisa Ash Sublett, Founder, Bleeding Kansas

“CBD works on receptors, and as it turns out, we have cannabinoids in our bodies, endogenous cannabinoids, that turn out to be very effective at regulating immune functions, nerve functions, bone functions,” stated Dr. Ethan Russo, a senior advisor to GW Pharmaceuticals, the British drug company that created a THC mouth spray known as Sativex.

“There’s a tendency to discount claims when something appears to be good for everything, but there’s a reason this is the case,” the doctor added, “the endogenous cannabinoid system acts as a modulator in fine-tuning a lot of these systems, and if something is deranged biochemically in a person’s body, it may well be that a cannabinoid system can bring things back into balance.”

I have compiled as much research as I could in the short amount of preparation time allowed. I would like the opportunity to provide even more research as I desire that no disease, condition, syndrome, etc. be excluded from access to this safe, non-toxic medication where research has proven efficacy.

I also note for you that some researchers, particularly Japanese researchers, have opted to use synthetic cannabinoids. In cases of cannabinoid receptors, full agonists can be dangerous. JWH-018 and other synthetic cannabinoids have been banned in nations around the world, including the US. This was after they were discovered in the contents of “incense” products, like Spice and K2, and connected to Psychosis and convulsions, among other conditions.

NOTE: We DO NOT endorse any use of synthetic cannabinoids for these reasons. We support whole plant, natural cannabinoids, which I believe as part of my personal faith, were created to fit our internal endocannabinoid system. Both, being made by the hand of a marvelous Creator.

Most patients do NOT prefer smoking as their delivery system. Many older studies from 1999 to 2007 may reference smoking as the delivery method used in their studies. Newer studies will utilize cannabis oils, microspheres, etc.

We support a certified “green” and organic process from start to finish, regulations, lab testing for quantifications, spectrometry and contaminants, to ensure patients have full disclosure and a safe product.

We desire this on the whole plant alone. Adjusting the levels and ratios of the over 85 compounds, or cannabinoids, can be achieved to personalize and individualize medication to a specific patient. This a wondrously novel and beneficial attribute of the cannabis whole plant approach or “Entourage Effect.”

All medications require adjustments and titrations, cannabis is no exception. But the plant was created with internal balances and controls, a harmony within the 85 cannabinoids. When we begin to synthesize, extract, and look for a way to mass produce some artificial medicine, we degrade the created and intentional balances, and lose those internal controls. - Lisa Ash Sublett, Founder, Bleeding Kansas

Steep Hill Halent Laboratories- Leading the Way in Cannabis Testing

<http://www.medicaljane.com/2014/03/01/steep-hill-halent-setting-high-standards-for-lab-testing-cannabis/>

Cytotoxicity is the quality of being toxic to cells. Examples of toxic agents are an immune cell or some types of venom, e.g. from the puff adder (*Bitis arietans*) or brown recluse spider (*Loxosceles reclusa*).

Cytotoxicity of synthetic cannabinoids found in "Spice" products: the role of cannabinoid receptors and the caspase cascade in the NG 108-15 cell line. <http://www.ncbi.nlm.nih.gov/pubmed/21907772>

Convulsions Associated with the Use of a Synthetic Cannabinoid Product
<http://link.springer.com/article/10.1007%2Fs13181-011-0182-2>

A searchable database

Clinical Studies and Case Reports

On this site you will find clinical studies with cannabis or single cannabinoids in different diseases and case reports on the use of cannabis by patients.

You may search for diseases (indications), authors, medication, study design (controlled study, open trial, case report etc.) and other criteria.

<http://www.cannabis-med.org/studies/study.php>

Microsphere Delivery System –Oil- Antitumor Effect

Spherical micro particles with a size range of 20-50 μm , and high entrapment efficiency (around 100%) were obtained. Cannabidiol (CBD) dissolved in the polymeric matrix of the microspheres was slowly released in vitro within 10 days. In vitro cell viability studies demonstrated the antitumoral activity of CBD released from microparticles. After 4 and 7 days of incubation, CBD in microspheres significantly inhibited the growth of MDA-MB-231 cells by 60% as compared to the 50% attained with free drug. The results suggest that PCL microparticles could be an alternative delivery system for long-term cannabinoid administration, showing potential therapeutic advantages over free drug.

<http://www.ncbi.nlm.nih.gov/pubmed/22580111>

News about therapeutic use of Cannabis and endocannabinoid system

Abstract

Growing basic research in recent years led to the discovery of the endocannabinoid system with a central role in neurobiology. New evidence suggests a therapeutic potential of cannabinoids in cancer chemotherapy-induced nausea and vomiting as well as in pain, spasticity and other symptoms in multiple sclerosis and movement disorders. Results of large randomized clinical trials of oral and sublingual Cannabis extracts will be known soon and there will be definitive answers to whether Cannabis has any therapeutic potential. Although the immediate future may lie in plant-based medicines, new targets for cannabinoid therapy focuses on the development of endocannabinoid degradation inhibitors which may offer site selectivity not afforded by cannabinoid receptor agonists.

<http://www.ncbi.nlm.nih.gov/pubmed/15033046>

Research into the workings of the endocannabinoid system has yielded significant discoveries for scientists attempting to learn more about pre and post-natal development.

It is apparent that endocannabinoids, chemical compounds produced in the body that are similar to the psychoactive ingredients in marijuana, act as a catalyst for early embryonic development and development thereafter into maturity. The same compounds have also been found at incredibly high concentrations in maternal breast milk, suggesting that cannabinoids are more important to our successful growth than was ever thought before. **“Endocannabinoids and their receptors are abundantly present from the early developmental stages, and are therefore likely to be important in the maturation of the nervous system and its functions.”**

The discovery of endocannabinoid production in human breast milk is certainly another nail in the coffin for those who subscribe to the theory that marijuana belongs in the same category as other class-1 narcotics. The occurrence and role of cannabinoids in breast milk has been the subject of multiple studies, and it is the belief of researchers that cannabinoids play an integral role in how babies learn to latch onto their mother’s nipple for sustenance.

It is theorized that, since cannabinoid activity has already been proven to be linked with appetite stimulation in adults, cannabinoids in breast milk are what first stimulate a nursing baby’s appetite. Cannabinoids, combined with other nutrients in breast milk, also provide the newborn with protection from viruses, bacteria, and cancer causing factors. This means that cannabinoids are quite literally essential in the development of infants.

These types of findings make the continued prohibition of marijuana seem utterly ludicrous. Cannabinoids are an integral part of our development and well-being from the time we are in our mother’s wombs, throughout the entirety of our lives.

<http://www.medicaljane.com/2013/02/13/cannabinoids-breast-milk-do-cannabinoids-play-a-larger-role-in-our-life-than-we-thought/>

http://www.safeaccessnow.org/cannabinoid_receptor_as_therapeutic_targets

http://www.safeaccessnow.org/the_emerging_role_of_the_endocannabinoid_system_in_endocrine_regulation_and_energy_balance

http://www.safeaccessnow.org/glossary_of_medical_terms

http://www.nap.edu/openbook.php?record_id=6376

<http://www.medicaljane.com/category/cannabis-classroom/ailment-research/>

http://www.safeaccessnow.org/resources_for_your_doctor_and_family

http://www.safeaccessnow.org/medical_cannabis_research_what_does_the_evidence_say

http://www.safeaccessnow.org/medical_professionals

Science: Cannabis smoking does not cause cancer according to a case-control study

<http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/does-smoking-cannabis-cause-cancer>

Cannabis and Its Derivatives: Review of Medical Use

Lawrence Leung, MBBChir, MFM(Clin)

Recent laboratory data highlight synergistic interactions between cannabinoid and opioid receptors, with potential reduction of drug-seeking behavior and opiate sparing effects.

<http://www.jabfm.org/content/24/4/452.abstract>

Cannabis and cannabinoids: pharmacology and rationale for clinical use.

Abstract

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.

<http://www.ncbi.nlm.nih.gov/pubmed/10575283>

Therapeutic potential of cannabinoid-based drugs.

Cannabinoids regulate many physiological functions and their impact on immunity is generally anti-inflammatory as powerful modulators of the cytokine cascade. This anti-inflammatory potency has led to the testing of these drugs in chronic inflammatory laboratory paradigms and even in some human diseases. Psychoactive and nonpsychoactive cannabinoid-based drugs such as Delta9-tetrahydrocannabinol, cannabidiol, HU-211, and ajulemic acid have been tested and found moderately effective in clinical trials of multiple sclerosis, traumatic brain injury, arthritis, and neuropathic pain. Furthermore, although clinical trials are not yet reported, preclinical data with cannabinoid-based drugs suggest efficacy in other inflammatory diseases such as inflammatory bowel disease, Alzheimer's disease, atherosclerosis, and osteoporosis.

<http://www.ncbi.nlm.nih.gov/pubmed/17713029>

Cannabinoid receptors in atherosclerosis

SUMMARY:

The immunomodulatory capacity of cannabinoids is now well established and suggests a broad therapeutic potential of cannabinoids for a variety of conditions, including atherosclerosis. New strategies based on nonpsychotropic cannabinoid receptor ligands or compounds modulating

endocannabinoid synthesis or stability might solve the problem of the unwanted side effects associated with cannabinoid administration.

<http://www.ncbi.nlm.nih.gov/pubmed/16960500>

Cannabinoids: mechanisms and therapeutic applications in the CNS.

Abstract

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 tumors. 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

<http://www.ncbi.nlm.nih.gov/pubmed/14529462>

Why we support whole plant and the “Entourage Effect” of cannabis

Cannabinoids in clinical practice.

Abstract

Cannabis has a potential for clinical use often obscured by unreliable and purely anecdotal reports. The most important natural cannabinoid is the psychoactive tetrahydrocannabinol (delta9-THC); others include cannabidiol (CBD) and cannabigerol (CBG). Not all the observed effects can be ascribed to THC, and the other constituents may also modulate its action; for **example CBD reduces anxiety induced by THC. A standardized extract of the herb may be therefore more beneficial in practice and clinical trial protocols have been drawn up to assess this.** The mechanism of action is still not fully understood, although cannabinoid receptors have been cloned and natural ligands identified. Cannabis is frequently used by patients with multiple sclerosis (MS) for muscle spasm and pain, and in an experimental model of MS low doses of cannabinoids alleviated tremor. Most of the controlled studies have been carried out with THC rather than cannabis herb and so do not mimic the usual clinical situation. Small clinical studies have confirmed the usefulness of THC as an analgesic; CBD and CBG also have analgesic and anti-inflammatory effects, indicating that there is scope for developing drugs which do not have the psychoactive properties of THC. Patients taking the synthetic derivative nabilone for neurogenic pain

actually preferred cannabis herb and reported that it relieved not only pain but the associated depression and anxiety. Cannabinoids are effective in chemotherapy-induced emesis and nabilone has been licensed for this use for several years. Currently, the synthetic cannabinoid HU211 is undergoing trials as a protective agent after brain trauma. Anecdotal reports of cannabis use include case studies in migraine and Tourette's syndrome, and as a treatment for asthma and glaucoma. Apart from the smoking aspect, the safety profile of cannabis is fairly good. However, adverse reactions include panic or anxiety attacks, which are worse in the elderly and in women, and less likely in children. Although psychosis has been cited as a consequence of cannabis use, an examination of psychiatric hospital admissions found no evidence of this, however, it may exacerbate existing symptoms. The relatively slow elimination from the body of the cannabinoids has safety implications for cognitive tasks, especially driving and operating machinery; although driving impairment with cannabis is only moderate, there is a significant interaction with alcohol. **Natural materials are highly variable and multiple components need to be standardized to ensure reproducible effects. Pure natural and synthetic compounds do not have these disadvantages but may not have the overall therapeutic effect of the herb.**

<http://www.ncbi.nlm.nih.gov/pubmed/11152013>

Anti-Inflammatory

Cannabinoids as novel anti-inflammatory drugs.

Manipulation of endocannabinoids and/or use of exogenous cannabinoids in vivo can constitute a potent treatment modality against inflammatory disorders. This review will focus on the potential use of cannabinoids as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components.

<http://www.ncbi.nlm.nih.gov/pubmed/20191092>

Immunoactive effects of cannabinoids: considerations for the therapeutic use of cannabinoid receptor agonists and antagonists.

Abstract

The active constituents of Cannabis sativa have been used for centuries as recreational drugs and medicinal agents. Today, marijuana is the most prevalent drug of abuse in the United States and, conversely, therapeutic use of marijuana constituents are gaining mainstream clinical and political acceptance. Given the documented contributions of endocannabinoid signaling to a range of physiological systems, including cognitive function, and the control of eating behaviors, it is unsurprising that cannabinoid receptor agonists and antagonists are showing significant clinical potential. In addition to the neuroactive effects of cannabinoids, an emerging body of data suggests that both endogenous and exogenous cannabinoids are potentially immunoactive. The central premise of this review article is that the immunological effects of cannabinoids should be considered in the context of each prescribing decision. We present evidence that the immunological effects of cannabinoid receptor agonists and antagonists are highly relevant to the spectrum of disorders for which cannabinoid therapeutics are currently offered.

<http://www.ncbi.nlm.nih.gov/pubmed/20219697>

Cannabis Deaths- FDA STATISTICS

Deaths from Marijuana v. 17 FDA-Approved Drugs

FDA Disclaimer of Information

Included in the 15 CDs and five printed reports from the FDA was the following disclosure:

"The information contained in the reports has not been scientifically or otherwise verified. For any given report there is no certainty that the suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions. The event may have been related to the underlying disease for which the drug was given to concurrent drugs being taken or may have occurred by chance at the same time the suspected drug was taken."

Numbers from these data must be carefully interpreted as reported rates and not occurrence rates. True incidence rates cannot be determined from this database. Comparisons of drugs cannot be made from these data."

-- July 18, 20/05 - FDA Office of Pharmacoepidemiology and Statistical Science, "Adverse Event Reporting System (AERS) Brief Description with Caveats of System"

[Editor's Note - ProCon.org makes no claim that the data below reflects occurrence rates. The information is presented for our readers' benefit who may feel that the relative comparisons have value. ProCon.org attempted to find the total number of users of each of these drugs by contacting the FDA, pharmaceutical trade organizations, and the actual drug manufacturers. We either did not receive a response or were told the information was proprietary or otherwise unavailable]

Summary of Deaths by Drug Classification

DRUG CLASSIFICATION	Specific Drugs per Category	Primary Suspect of the Death	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
A. MARIJUANA <i>also known as: Cannabis sativa L</i>	Marijuana Cannabis Cannabinoids	0	279	279
B. ANTI-EMETICS <i>(used to treat vomiting)</i>	Compazine Reglan Marinol Zofran Anzemet Kytril Tigan	196	429	625
C. ANTI-SPASMODICS <i>(used to treat muscle spasms)</i>	Baclofen Zanaflex	118	56	174

D. ANTI-PSYCHOTICS (used to treat psychosis)	Haldol Lithium Neurontin	1,593	702	2,295
E. OTHER POPULAR DRUGS (used to treat various conditions including ADD, depression, narcolepsy, erectile dysfunction, and pain)	Ritalin Wellbutrin Adderall Viagra Vioxx*	8,101	492	8,593
F. TOTALS of A-E	Number of Drugs in Total	Primary Suspect of the Death	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
• TOTAL DEATHS FROM MARIJUANA	1	0	279	279
• TOTAL DEATHS FROM 17 FDA-APPROVED DRUGS	17	10,008	1,679	11,687

V. Chart of Deaths from Marijuana and 17 FDA-Approved Drugs

A. Marijuana				
DRUG (Year Approved)		Primary Suspect of the Death	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
1.	Marijuana (not approved) <i>also known as: Cannabis sativa L</i>	0	109	109
2.	Cannabis (not approved) <i>also known as: Cannabis sativa L</i>	0	78	78
3.	Cannabinoids (unclear if these mentions include non-plant cannabinoids)	0	92	92
Sub-Total - Anti-Emetics		0	279	279

FDA-Approved Drugs Prescribed in Place of Medical Marijuana

B. Anti-Emetics

DRUG (Year Approved)		Primary Suspect of the Death	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
1.	Compazine (1980) <i>also known as: Phenothiazine, prochlorperazine</i>	15	30	45
2.	Reglan (1980) <i>also known as: Metaclopramide, Paspertin, Primperan</i>	37	278	315
3.	Marinol (1985) <i>also known as: Dronabinol</i>	4	1	5
4.	Zofran (1991) <i>also known as: Ondansetron hydrochloride</i>	79	76	155
5.	Anzemet (1997) <i>also known as: Dolasetron mesylate</i>	22	5	27
6.	Kytril (1999) <i>also known as: Granisetron hydrochloride</i>	36	24	60
7.	Tigan (2001) <i>also known as: Trimethobenzamide</i>	3	15	18
Sub-Total - Anti-Emetics		196	429	625

C. Anti-Spasmodics

DRUG (Year Approved)		Primary Suspect of the Death	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
1.	Baclofen (1967) <i>also known as: Lioresal, 4-amino-3-(4-chlorophenyl)-butanoic acid</i>	72	33	105
2.	Zanaflex (1996) <i>also known as: Tizanidine hydrochloride, Sirdalud, Ternelin</i>	46	23	69
Sub-Total - Anti-Spasmodics		118	56	174

D. Anti-Psychotics

DRUG (Year Approved)		Primary Suspect of the	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 -
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		Death		6/30/05
1.	Haldol (1967) <i>also known as: Haloperidol, Haldol Decanoate, Serenace, Halomonth</i>	450	267	717
2.	Lithium (1970) <i>also known as: Lithium Carbonate, Eskalith, Lithobid, Lithonate, Teralithe, Lithane, Hypnorex, Limas, Lithionit, Quilonum</i>	175	133	308
3.	Neurontin (1994) <i>also known as: Gabapentin</i>	968	302	1,270
Sub-Total - Anti-Psychotics		1,593	702	2,295


E. Other Well-Known and Randomly Selected FDA-Approved Drugs

DRUG (Year Approved)		Primary Suspect of the Death	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
1.	Ritalin (1955) <i>also known as: Methylphenidate, Concerta, Medadate, Ritaline (used to treat ADD and ADHD)</i>	121	53	174
2.	Wellbutrin (1997) <i>also known as: Bupropion Hydrochloride, Zyban, Zynatabac, Amfebutamone (used to treat depression & anxiety)</i>	1,132	220	1,352
3.	Adderall (1966) <i>also known as: Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate USP, Amphetamine Sulfate USP (used to treat narcolepsy or to control hyperactivity in children)</i>	54	12	66
4.	Viagra (1998) <i>also known as: Sildenafil Citrate (used to treat erectile dysfunction)</i>	2,254	40	2,294
5.	Vioxx* (1999)	4,540	167	4,707

	also known as: <i>Rifecixub</i> , <i>Arofexx</i> (used to treat osteoarthritis and pain)			
Sub-Total - Other Popular Drugs		8,101	492	8,593
F. TOTALS of A-E		Primary Suspect	Secondary Suspect(Contributing to death)	Total Deaths Reported 1/1/97 - 6/30/05
• TOTAL DEATHS FROM MARIJUANA		0	279	279
• TOTAL DEATHS FROM 17 FDA-APPROVED DRUGS		10,008	1,679	11,687

*[**Editor's Note:** Merck, the maker of Vioxx, publicly announced its voluntary withdrawal of Vioxx from the global market on September 30, 2004. In 2005, advisory panels in both the US and Canada encouraged the return of Vioxx to the market, stating that Vioxx's benefits outweighed the risks for some patients. The FDA advisory panel voted 17-15 to allow the drug to return to the market despite being found to increase heart risk. The vote in Canada was 12-1, and the Canadian panel noted that the cardiovascular risks from Vioxx seemed to be no worse than those from ibuprofen. Notwithstanding these recommendations, Merck has not returned Vioxx to the market as of July

<http://medicalmarijuana.procon.org/view.resource.php?resourceID=0001>

The Substance Abuse and Mental Health Services Administration's (SAMHSA) 2003 report [Mortality Data from the Drug Abuse Warning Network, 2001](#) (1.5 MB)  stated:

"Marijuana is rarely the only drug involved in a drug abuse death. Thus ... the proportion of marijuana-induced cases labeled as 'One drug' (i.e., marijuana only) will be zero or nearly zero."

2003 - [Substance Abuse and Mental Health Services Administration](#) ★

http://www.drugwarfacts.org/cms/causes_of_death#sthash.QDrzKIMZ.dpbs

Joycelyn Elders, MD, former US Surgeon General, wrote the following in her Mar. 26, 2004 editorial published in the *Providence Journal*:

"Unlike many of the drugs we prescribe every day, marijuana has never been proven to cause a fatal overdose."

Mar. 26, 2004 - [Joycelyn Elders, MD](#) ★★★★★

Cannabis Risks- "Although centuries of human experimentation tells us that naturally-occurring cannabinoids are broadly safe, they are not without risks. They can increase the heart rate, which may cause problems for patients with pre-existing or undiagnosed heart conditions. They can also interact

with other drugs in the body, including antidepressants and antihistamines. And they may also affect how the body processes certain chemotherapy drugs, which could cause serious side effects.”

<http://scienceblog.cancerresearchuk.org/2012/07/25/cannabis-cannabinoids-and-cancer-the-evidence-so-far/>

As side-effects go, I hear far worse, many times a day, on commercials running on my television. All for FDA approved drugs. These risks would be properly mitigated and assessed under proper medical supervision and screening, as with all other medications. It is when we force patients to the criminal black market that their risks for any complications, whether by pesticide, contaminant, mold, mites, or violence, all increase exponentially. Safe, legal and medically monitored access will protect patients on many, various levels. – Lisa Ash Sublett- Founder, Bleeding Kansas. “My Two Cents”

<http://www.histmodbiomed.org/sites/default/files/44870.pdf>

The Highs and Lows of Cannabinoid Receptor Expression in Disease: Mechanisms and Their Therapeutic Implications

<http://pharmrev.aspetjournals.org/content/63/3/461.abstract>

Neurodegenerative Disease

Neurodegenerative diseases occur when nervous system cells (neurons) in the brain and spinal cord begin to deteriorate. Changes in these cells cause them to function abnormally and eventually result in the cells' demise. As neurons deteriorate, an individual may first experience relatively mild symptoms — problems with coordination or remembering names. But as huge numbers of neurons die, symptoms progressively worsen. In some cases, patients lose the ability to walk independently, think clearly, or generally function in the world. Ultimately, many of these diseases are fatal.

Today, 5 million Americans suffer from Alzheimer's disease; 1 million from Parkinson's; 400,000 from multiple sclerosis (MS); 30,000 from amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), and 30,000 from Huntington's disease. Because neurodegenerative diseases strike primarily in mid- to late-life, the incidence is expected to soar as the population ages. (By 2030, as many as 1 in 5 Americans will be over the age of 65.) If left unchecked 30 years from now, more than 12 million Americans will suffer from neurodegenerative diseases. Finding treatments and cures for neurodegenerative diseases is a goal of increasing urgency.

http://www.neurodiscovery.harvard.edu/challenge/challenge_2.html

<http://www.medicaljane.com/2014/11/11/cannabis-classroom-neurodegenerative-disease-and-medical-marijuana/>

<http://onlinelibrary.wiley.com/doi/10.1111/bph.12492/pdf>

<http://rstb.royalsocietypublishing.org/content/367/1607/3326.full.pdf+html>

<http://www.ncbi.nlm.nih.gov/pubmed/25042014>

<http://www.medicaljane.com/2014/08/06/study-ultra-low-doses-of-thc-may-help-protect-against-neurodegenerative-diseases/>

According to the researchers, "These findings suggest that prolonged administration of cannabinoid receptor agonists could be an appropriate strategy for selectively improving motor symptoms and stimulating neuroprotective processes in patients with Huntington's disease." Given the severely debilitating nature of motor symptoms caused by Huntington's disease and a limited set of possible treatment options, the results of this study warrant increased research into the utility of cannabinoid therapies for patients with Huntington's disease. <http://www.ncbi.nlm.nih.gov/pubmed/25123645>

Endocannabinoids act as neuromodulator and neuroprotective cues by engaging type 1 cannabinoid receptors. These receptors are highly abundant in the basal ganglia and play a pivotal role in the control of motor behavior. An early down regulation of type 1 cannabinoid receptors has been documented in the basal ganglia of patients with Huntington's disease and animal models. However, the pathophysiological impact of this loss of receptors in Huntington's disease is as yet unknown. Here, we generated a double-mutant mouse model that expresses human mutant huntingtin exon 1 in a type 1 cannabinoid receptor-null background, and found that receptor deletion aggravates the symptoms, neuropathology and molecular pathology of the disease. Moreover, pharmacological administration of the cannabinoid Δ^9 -tetrahydrocannabinol to mice expressing human mutant huntingtin exon 1 exerted a therapeutic effect and ameliorated those parameters. Experiments conducted in striatal cells show that the mutant huntingtin-dependent down regulation of the receptors involves the control of the type 1 cannabinoid receptor gene promoter by repressor element 1 silencing transcription factor and sensitizes cells to excitotoxic damage. We also provide *in vitro* and *in vivo* evidence that supports type 1 cannabinoid receptor control of striatal brain-derived neurotrophic factor expression and the decrease in brain-derived neurotrophic factor levels concomitant with type 1 cannabinoid receptor loss, which may contribute significantly to striatal damage in Huntington's disease. Altogether, these results support the notion that down regulation of type 1 cannabinoid receptors is a key pathogenic event in Huntington's disease, and suggest that activation of these receptors in patients with Huntington's disease may attenuate disease progression.

<http://brain.oxfordjournals.org/content/early/2010/10/07/brain.awq278.abstract>

Science: Alzheimer's disease

Researchers of the University of Naples in Italy found that the natural cannabidiol (CBD) protected nerve cells against the toxicity caused by amyloid-beta. Amyloid-beta peptide plays an important role in Alzheimer's disease, since increased brain levels of amyloid-beta are supposed to result in aggregation of this protein to form "plaques" found in the brain of sufferers of Alzheimer's disease. Earlier research already had shown that the endocannabinoids anandamide and noladin ether prevent the toxicity of amyloid-beta. (Source: Iuvone T, et al. J Neurochem. 2004 Apr;89(1):134-41.)

Therapeutic potential of cannabinoids in CNS disease.

Abstract

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 tumor necrosis factor suggests that they may be potent neuroprotective agents. Dexamabinol (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 cancer 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 dexamabinol 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.

<http://www.ncbi.nlm.nih.gov/pubmed/12617697>

An Overview of Alzheimer's disease and Medical Marijuana

"THC could be a potential therapeutic treatment option for Alzheimer's disease through multiple functions and pathways."

<http://www.medicaljane.com/2014/11/17/alzheimers-disease-and-medical-marijuana/>

	CB ₁ receptor	CB ₂ receptor	Endocannabinoid levels	Endocannabinoid synthesis	Endocannabinoid degradation
Alzheimer's disease	CB ₁ receptor expression initially rises followed by decline during disease progression (Farkas <i>et al.</i> , 2012). CB ₁ receptor functionally impaired (Ramirez <i>et al.</i> , 2005).	CB ₂ receptor expression increases in the entorhinal cortex and parahippocampus (Benito <i>et al.</i> , 2003; Solas <i>et al.</i> , 2013).	Decreased AEA levels in the midfrontal and temporal cortex (Jung <i>et al.</i> , 2012).	DGLα and DGLβ levels are increased in AD patients (Braak stage IV) (Mulder <i>et al.</i> , 2011).	Increased FAAH levels (Benito <i>et al.</i> , 2003). Increased MGL levels in AD patients (Braak stage IV) (Mulder <i>et al.</i> , 2011).

Molecular and Cellular Neuroscience

Volume 56, September 2013, Pages 255–262 RNA and splicing regulation in neurodegeneration

Role of the cannabinoid system in the transit of beta-amyloid across the blood–brain barrier

Abstract

Emerging evidence suggests beta-amyloid (A β) deposition in the Alzheimer's disease (AD) brain is the result of impaired clearance, due in part to diminished A β transport across the blood–brain barrier (BBB). Recently, modulation of the cannabinoid system was shown to reduce A β brain levels and improve cognitive behavior in AD animal models. The purpose of the current studies was to investigate the role of the cannabinoid system in the clearance of A β across the BBB. Using in vitro and in vivo models of BBB clearance, A β transit across the BBB was examined in the presence of cannabinoid receptor agonists and inhibitors. In addition, expression levels of the A β transport protein, lipoprotein receptor-related protein1 (LRP1), were determined in the brain and plasma of mice following cannabinoid treatment. Cannabinoid receptor agonism or inhibition of endocannabinoid-degrading enzymes significantly enhanced A β clearance across the BBB (2-fold). Moreover, cannabinoid receptor inhibition negated the stimulatory influence of cannabinoid treatment on A β BBB clearance. Additionally, LRP1 levels in the brain and plasma were elevated following cannabinoid treatment (1.5-fold), providing rationale for the observed increase in A β transit from the brain to the periphery. The current studies demonstrate, for the first time, a role for the cannabinoid system in the transit of A β across the BBB. These findings provide insight into the mechanism by which cannabinoid treatment reduces A β burden in the AD brain and offer additional evidence on the utility of this pathway as a treatment for AD.

<http://www.sciencedirect.com/science/article/pii/S104474311300064X>

Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1 Δ E9 mice

Abstract

Rationale

Patients suffering from Alzheimer's disease (AD) exhibit a decline in cognitive abilities including an inability to recognize familiar faces. Hallmark pathological changes in AD include the aggregation of amyloid- β (A β), tau protein hyper phosphorylation as well as pronounced neurodegeneration, neuroinflammation, neurotoxicity and oxidative damage.

Objectives

The non-psychoactive phytocannabinoid cannabidiol (CBD) exerts neuroprotective, anti-oxidant and anti-inflammatory effects and promotes neurogenesis. CBD also reverses A β -induced spatial memory deficits in rodents.

Materials and methods

Thus we determined the therapeutic-like effects of chronic CBD treatment (20 mg/kg, daily intraperitoneal injections for 3 weeks) on the APPswe/PS1 Δ E9 (APPxPS1) transgenic mouse model for AD in a number of cognitive tests, including the social preference test, the novel object recognition task and the fear conditioning paradigm. We also analysed the impact of CBD on anxiety behaviors in the elevated plus maze.

Results

Vehicle-treated APPxPS1 mice demonstrated impairments in social recognition and novel object recognition compared to wild type-like mice. Chronic CBD treatment reversed these cognitive deficits in APPxPS1 mice without affecting anxiety-related behaviors.

Conclusions

This is the first study to investigate the effect of chronic CBD treatment on cognition in an AD transgenic mouse model. Our findings suggest that CBD may have therapeutic potential for specific cognitive impairments associated with AD.

<http://link.springer.com/article/10.1007%2Fs00213-014-3478-5>

Blocking brain's 'internal marijuana' may trigger early Alzheimer's deficits, study shows

A-beta, a substance suspected as a prime culprit in Alzheimer's disease, may start impairing learning and memory long before plaques form in the brain.

A substance called A-beta — strongly suspected to play a key role in Alzheimer's because it's the chief constituent of the hallmark clumps dotting the brains of people with Alzheimer's — may, in the disease's earliest stages, impair learning and memory by blocking the natural, beneficial action of endocannabinoids in the brain, the study demonstrates. The Stanford group is now trying to figure out the molecular details of how and where this interference occurs. Pinning down those details could pave the path to new drugs to stave off the defects in learning ability and memory that characterize Alzheimer's.

In the study, published June 18 in *Neuron*, researchers analyzed A-beta's effects on a brain structure known as the hippocampus. In all mammals, this midbrain structure serves as a combination GPS system and memory-filing assistant, along with other duties.

"The hippocampus tells us where we are in space at any given time," said Daniel Madison, PhD, associate professor of molecular and cellular physiology and the study's senior author. "It also processes new experiences so that our memories of them can be stored in other parts of the brain. It's the filing secretary, not the filing cabinet."

<http://med.stanford.edu/news/all-news/2014/06/blocking-brain-s-internal-marijuana-may-trigger-early-alzheimers.html>

The Potential Therapeutic Effects of THC on Alzheimer's Disease

Journal **Journal of Alzheimer's Disease**

Abstract

The purpose of this study was to investigate the potential therapeutic qualities of Δ^9 -tetrahydrocannabinol (THC) with respect to slowing or halting the hallmark characteristics of Alzheimer's disease. N2a-variant amyloid- β protein precursor (A β PP) cells were incubated with THC and assayed for amyloid- β (A β) levels at the 6-, 24-, and 48-hour time marks. THC was also tested for synergy with caffeine, in respect to the reduction of the A β level in N2a/A β PPswe cells. THC was also tested to determine if multiple treatments were beneficial. The MTT assay was performed to test the toxicity of THC. Thioflavin T assays and western blots were performed to test the direct anti-A β aggregation significance of THC. Lastly, THC was tested to determine its effects on glycogen synthase

kinase-3 β (GSK-3 β) and related signaling pathways. From the results, we have discovered THC to be effective at lowering A β levels in N2a/A β PPswe cells at extremely low concentrations in a dose-dependent manner. However, no additive effect was found by combining caffeine and THC together. We did discover that THC directly interacts with A β peptide, thereby inhibiting aggregation. Furthermore, THC was effective at lowering both total GSK-3 β levels and phosphorylated GSK-3 β in a dose-dependent manner at low concentrations. At the treatment concentrations, no toxicity was observed and the CB1 receptor was not significantly upregulated. Additionally, low doses of THC can enhance mitochondria function and does not inhibit melatonin's enhancement of mitochondria function. These sets of data strongly suggest that THC could be a potential therapeutic treatment option for Alzheimer's disease through multiple functions and pathways.

<http://iospress.metapress.com/content/8421pvx80144t354/?genre=article&id=doi%3a10.3233%2fJAD-140093>

MS

My Note *Most patients do NOT prefer smoking as a delivery method. We do NOT support the use of synthetic cannabinoids.

Role of cannabinoids in multiple sclerosis.

Abstract

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.

<http://www.ncbi.nlm.nih.gov/pubmed/21323391>

Cannabis and Amyotrophic Lateral Sclerosis: Hypothetical and Practical Applications, and a Call for Clinical Trials

AM J HOSP PALLIAT CARE August 2010 27: 347-356, first published on May 3, 2010

<http://ajh.sagepub.com/content/27/5/347.full.pdf+html>

Cannabinoids in the treatment of pain and spasticity in multiple sclerosis.

<http://www.ncbi.nlm.nih.gov/pubmed/12137404>

Cannabinoids and multiple sclerosis

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).

<http://www.ncbi.nlm.nih.gov/pubmed/12182963>

Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial

<http://www.cmaj.ca/content/184/10/1143.abstract>

Towards cannabis and cannabinoid treatment of multiple sclerosis.

Abstract

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.

<http://www.ncbi.nlm.nih.gov/pubmed/15510238>

Cannabinoids in multiple sclerosis: do they have a therapeutic role?

Abstract

This is an exciting time for cannabinoid research. Evidence suggests that cannabis (marijuana) can alleviate symptoms like muscle spasticity and pain in patients with multiple sclerosis (MS). Interest in the field of cannabinoids has been strengthened by the identification and cloning of cannabinoid receptors located in the central nervous system and the peripheral immune organs, and by the discovery of the endogenous cannabinoid ligands. Cannabinoids are also efficacious in animal models of MS.

<http://www.ncbi.nlm.nih.gov/pubmed/14723555>

Cannabinoids control spasticity and tremor in a multiple sclerosis model

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.

<http://www.ncbi.nlm.nih.gov/pubmed/10716447el>.

The role of cannabinoid system on immune modulation: therapeutic implications on CNS inflammation

Abstract

There is a growing amount of evidence suggesting that cannabinoids may be neuroprotective in CNS inflammatory conditions. Advances in the understanding of the physiology and pharmacology of the cannabinoid system have increased the interest of cannabinoids as potential therapeutic targets. Cannabinoid receptors and their endogenous ligands, the endocannabinoids, have been detected in cells of the immune system, as well as in brain glial cells. In the present review it is summarized the effects of cannabinoids on immune reactivity and on the regulation of neuroinflammatory processes associated with brain disorders with special attention to chronic inflammatory demyelinating diseases such as multiple sclerosis.

<http://www.ncbi.nlm.nih.gov/pubmed/16026313>

Arthritis

Before diving into the study, it's helpful to know that [fibroblast-like synoviocytes \(FLS\)](#) are the type of cells most often associated with Rheumatoid Arthritis. They become constantly engaged in inflammatory mechanisms, which causes cartilage damage, joint destruction, and deformation over time.

CONCLUSION: In RA-FLS, proinflammatory mediators up-regulate the expression of CB2R, which negatively regulates the production of proinflammatory cytokines and MMPs. These data suggest that CB2R may be a potential therapeutic target of RA.

<http://www.ncbi.nlm.nih.gov/pubmed/24440992>

Cannabis infused topicals are a common method of treatment for joint pain, because they allow patients to target the areas in need of the most relief.

Osteoarthritis is a degenerative joint disease associated with articular cartilage degradation. The major clinical outcome of osteoarthritis is a complex pain state that includes both nociceptive and neuropathic mechanisms. Currently, the therapeutic approaches for osteoarthritis are limited as no drugs are available to control the disease progression and the analgesic treatment has restricted efficacy. Increasing evidence from preclinical studies supports the interest of the endocannabinoid system as an emerging therapeutic target for osteoarthritis pain. Indeed, pharmacological studies have shown the anti-nociceptive effects of cannabinoids in different rodent models of osteoarthritis, and compelling evidence suggests an active participation of the endocannabinoid system in the pathophysiology of this disease. The ubiquitous distribution of cannabinoid receptors, together with the physiological role of the endocannabinoid system in the regulation of pain, inflammation and even joint function further support the therapeutic interest of cannabinoids for osteoarthritis. However, limited clinical evidence has been provided to support this therapeutic use of cannabinoids, despite the promising preclinical data. This review summarizes the promising results that have been recently obtained in support of the therapeutic value of cannabinoids for osteoarthritis management.

<http://www.ncbi.nlm.nih.gov/pubmed/24494687>

Cancer

San Francisco, CA, December 13, 2012– Researchers at California Pacific Medical Center Research Institute (CPMCRI, a Sutter Health affiliate) have found that a compound in cannabis previously shown to decrease metastatic breast cancer now shows promise in stopping aggressive brain cancer as well. The findings are particularly important given the safety of the cannabis compound and the fact that patients with advanced brain cancer have few options for treatment.

“These findings offer some hope in an area where there’s been very little, and give even greater potential to our earlier research,” said Pierre-Yves Desprez, Ph.D., senior scientist with CPMCRI and corresponding author of the new study. “We thought that the mechanisms for the progression of brain cancer would be quite different from that of breast and other cancers, and the fact that we were able to duplicate the same success for brain cancer that we did for breast, quite frankly, amazed us.”

There are about 20,000 people diagnosed with brain cancer each year in the US alone, and very few therapies exist to help those with the most aggressive form of the disease. Brain tumors, known as gliomas, are the fourth most frequent cause of cancer-related death in younger patients aged 35 – 45; the median survival span from the time of diagnosis is 14 months. And the incidence of the most malignant type of tumor, glioblastoma, appears to be on the rise.

<http://www.cpmc.org/about/press/news2012/cannabis-brain.html>

The new study in Cancer Research, entitled "Id-1 is a Key Transcriptional Regulator of Glioblastoma Aggressiveness and a Novel Therapeutic Target," can be found online at the website of the American Association for Cancer Research.

Abstract

The G protein-coupled receptors CB2 (CB2R) and GPR55 are overexpressed in cancer cells and human tumors. Because a modulation of GPR55 activity by cannabinoids has been suggested, we analyzed whether this receptor participates in cannabinoid effects on cancer cells. Here we show that CB2R and GPR55 form heteromers in cancer cells, that these structures possess unique signaling properties, and that modulation of these heteromers can modify the antitumoral activity of cannabinoids *in vivo*. These findings unveil the existence of previously unknown signaling platforms that help explain the complex behavior of cannabinoids and may constitute new targets for therapeutic intervention in oncology.

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<http://www.ncbi.nlm.nih.gov/pubmed/24942731>

Various reports have shown that cannabinoids (the active components of marijuana and their derivatives) can reduce tumor growth and progression in animal models of cancer, in addition to their well-known palliative effects on some cancer-associated symptoms. This Opinion article discusses our current understanding of cannabinoids as antitumor agents, focusing on recent insights into the molecular mechanisms of action, including emerging resistance mechanisms and opportunities for combination therapy approaches. Such knowledge is required for the optimization of preclinical cannabinoid-based therapies and for the preliminary clinical testing that is currently underway.

<http://www.ncbi.nlm.nih.gov/pubmed/22555283>

<http://www.medicaljane.com/2014/01/09/study-cannabis-extracts-rich-in-cannabidiol-cbd-may-effectively-treat-colon-cancer/>

Δ^9 -Tetrahydrocannabinol (THC) and other cannabinoids inhibit tumor growth and angiogenesis in animal models, so their potential application as antitumoral drugs has been suggested. However, the antitumoral effect of cannabinoids has never been tested in humans. Here we report the first clinical study aimed at assessing cannabinoid antitumoral action, specifically a pilot phase I trial in which nine patients with recurrent glioblastoma multiforme were administered THC intratumorally. The patients had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumor progression. The primary end point of the study was to determine the safety of intracranial THC administration. We also evaluated THC action on the length of survival and various tumor-cell parameters. A dose escalation regimen for THC administration was assessed. Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval: 15–33). Δ^9 -Tetrahydrocannabinol inhibited tumor-cell proliferation *in vitro* and decreased tumor-cell Ki67 immunostaining when administered to two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumor cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

<http://www.nature.com/bjc/journal/v95/n2/full/6603236a.html>

Inhibition of human tumor prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2

We have previously shown that cannabinoids induce growth inhibition and apoptosis in prostate cancer PC-3 cells, which express high levels of cannabinoid receptor types 1 and 2 (CB1 and CB2). In this study, we investigated the role of CB2 receptor in the anti-proliferative action of cannabinoids and the signal transduction triggered by receptor ligation.

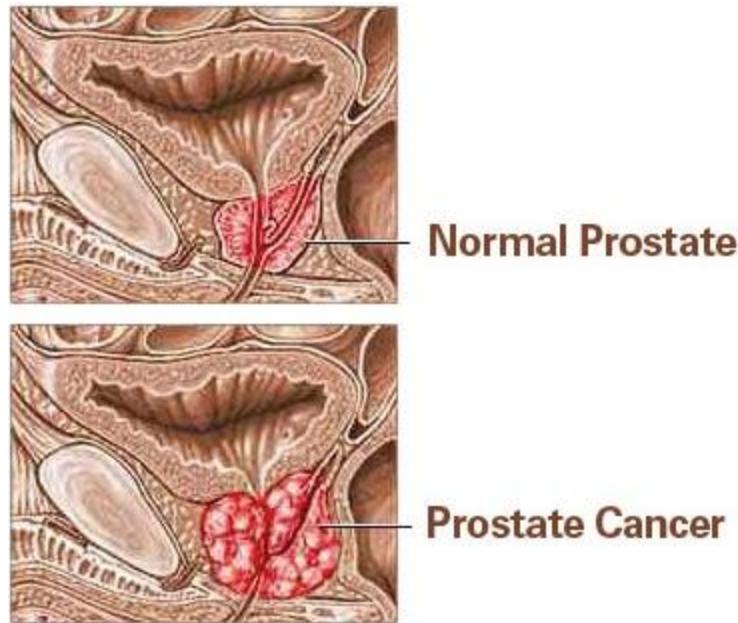
conclusions: This study defines the involvement of CB2-mediated signaling in the in vivo and in vitro growth inhibition of prostate cancer cells and suggests that CB2 agonists have potential therapeutic interest and deserve to be explored in the management of prostate cancer.

<http://www.nature.com/bjc/journal/v101/n6/full/6605248a.html>

Prostate cancer has become the most common cancer diagnosed in men and is one of the major life-threatening diseases in Western countries (Ukrainitseva et al, 2008). Despite recent advances in its diagnosis and treatment, current therapies are unable to completely eliminate the androgen-independent prostate cancer cells that remain after androgen ablation therapy (Bahnsen, 2007). Thus, understanding the mechanisms involved in the control of tumor growth and the development of chemo preventive agents are major goals of basic research in oncology.

Cannabinoids, the active components of *Cannabis sativa* and their derivatives, exert a wide spectrum of modulatory actions and pharmacological activities in the brain as well as in the periphery, and therefore, the therapeutic potential of cannabinoids has gained much attention during the past few years (Kogan and Mechoulam, 2007). One of the most exciting areas of current research in the therapeutic potential of cannabinoids is cancer. Recent evidence suggests that cannabinoids are powerful regulators of cell growth and differentiation. They have been shown to exert anti-humoral effects by decreasing viability, proliferation, adhesion and migration on various cancer cells, thereby suggesting the potential use of cannabinoids in the treatment of gliomas, prostate and breast cancers and malignancies of immune origin (Bifulco et al, 2006; Flygare and Sander, 2008; Sarfaraz et al, 2008; Pisanti et al, 2009). The mechanisms of the anti-humoral action of cannabinoids include inhibition of tumor cell proliferation, induction of cell death, inhibition of cell migration and metastasis, anti-angiogenic effects and modulation of immune response (Guzman, 2003; Flygare and Sander, 2008). Various cannabinoids, especially anandamide and THC, promote apoptosis of astrocytoma, glioma, neuroblastoma and pheochromocytoma cells in culture by a pathway involving cannabinoid receptors (Guzman, 2003; Goncharov et al, 2005; Velasco et al, 2007) and by an activation of the reticulum stress pathway (Carracedo et al, 2006b; Salazar et al, 2009a).

<http://www.nature.com/bjc/journal/v101/n6/full/6605248a.html>



<http://www.medicaljane.com/ailment/prostate-cancer/>

"CB2 agonists have potential therapeutic interest and deserve to be explored in the management of prostate cancer." – Professor I Díaz-Laviada

<http://www.medicaljane.com/2014/01/17/study-medical-cannabis-may-inhibit-the-spread-of-prostate-cancer/>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901602/>

Inhibition of human tumor prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2

conclusions: This study defines the involvement of CB2-mediated signaling in the in vivo and in vitro growth inhibition of prostate cancer cells and suggests that CB2 agonists have potential therapeutic interest and deserve to be explored in the management of prostate cancer.

<http://www.nature.com/bjc/journal/v101/n6/full/6605248a.html>

Fig. 6

Response to hemp oil treatment over 78 days.

The results shown here cannot be attributed to the phenomenon of 'spontaneous remission' because a dose response curve was achieved. Three factors, namely frequency of dosing, amount given (therapeutic dosing) and the potency of the cannabis strains, were critical in determining response and disease control. In the figure, it can be seen that introducing strains that were less potent, dosing at intervals >8 h and suboptimal therapeutic dosing consistently showed increases in the leukemic blast cell count. It could not be determined which cannabinoid profiles

constituted a ‘potent’ cannabis strain because the resin was not analyzed. Research is needed to determine the profile and ratios of cannabinoids within the strains that exhibit antileukemic properties.

These results cannot be explained by any other therapies, as the child was under palliative care and was solely on cannabinoid treatment when the response was documented by the SickKids Hospital. The toxicology reports ruled out chemotherapeutic agents, and only showed her to be positive for THC (tetrahydrocannabinol) when she had ‘a recent massive decrease of WBC from 350,000 to 0.3’ inducing tumor lysis syndrome, as reported by the primary hematologist/oncologist at the SickKids Hospital.

This therapy has to be viewed as polytherapy, as many cannabinoids within the resinous extract have demonstrated targeted, antiproliferative, proapoptotic and antiangiogenic properties. This also needs to be explored further, as there is potential that cannabinoids might show selectivity when attacking cancer cells, thereby reducing the widespread cytotoxic effects of conventional chemotherapeutic agents. It must be noted that where our most advanced chemotherapeutic agents had failed to control the blast counts and had devastating side effects that ultimately resulted in the death of the patient, the cannabinoid therapy had no toxic side effects and only psychosomatic properties, with an increase in the patient's vitality.

The nontoxic side effects associated with cannabis may be minimized by slowly titrating the dosing regimen upwards, building up the patient's tolerance. The possibility of bypassing the psychoactive properties also exists, by administering nonpsychoactive cannabinoids such as cannabidiol that have demonstrated antiproliferative properties. Furthermore, future therapies could examine the possibility of upregulating a patient's endogenous cannabinoids to help combat leukemic cells. It goes without saying that much more research and, even more importantly, phase clinical trials need to be implemented to determine the benefits of such therapies. Laboratory analysis is critical to figure out the constituents/profiles/ratios of the vast cannabis strains that show the most favored properties for exerting possible anticancer effects. Despite the nonstandardization of the medicines, the dose was readily titrated according to the biological response of the patient and produced a potentially life-saving response, namely, the drop in the leukemic blast cell count.

There has been an abundance of research exhibiting the cytotoxic effects of cannabinoids on leukemic cell lines in the form of in vitro and in vivo studies [1, 2, 3, 4]. An oncology and hematology journal, *Blood*, has published numerous papers [2] over the years constructing the biochemical pathway to be elicited by the anticancer properties of cannabinoids. Our goal, upon examination of this significant case study which demonstrated complete disease control and a dose response curve, is to invest effort in and to focus on research and development to advance this therapy. An emphasis needs to be placed on determining the correct cannabinoid ratios for different types of cancer, the best method of administration, quality control and standardization

of the cannabis strains and their growing conditions as well as therapeutic dosing ranges for various cancers contingent on staging and ages. Toxicity profiles favor therapies deriving from cannabis because toxicity within the body is greatly reduced and the devastating side effects of chemoradiation (i.e. secondary cancers or death) can be eliminated. It is unfortunate that this therapy does come with some unwanted psychosomatic properties; however, these might be eliminated by target therapies of nonpsychoactive cannabinoids such as cannabidiol which has garnered much attention as being a potent anti-inflammatory and possible antileukemic and anticancer agent. It is acknowledged that significant research needs to be conducted to reproduce these results and that in vitro studies cannot always be reproduced in clinical trials and the human physiological microenvironment. However, the numerous research studies and this particular clinical case are powerful enough to warrant implementing clinical trials to determine dose ranges, cannabinoid profiles and ratios, the methods of administration that produce the most efficacious therapeutic responses and the reproducibility of the results. It is tempting to speculate that, with integration of this care in a setting of full medical and laboratory support, a better outcome may indeed be achieved in the future.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901602/>

Abstract

The medicinal properties of extracts from the hemp plant *Cannabis sativa* have been known for centuries but only in the 90s membrane receptors for the Cannabis major principle were discovered in mammalian cells. Later on the endogenous ligands for the cannabinoid receptors were identified and the term 'endocannabinoid system' was coined to indicate the complex signaling system of cannabinoid receptors, endogenous ligands and the enzymes responsible for their biosynthesis and inactivation. The 'endocannabinoid system' is involved in a broad range of functions and in a growing number of pathological conditions. There is increasing evidence that endocannabinoids are able to inhibit cancer cell growth in culture as well as in animal models. Most work has focused on the role of endocannabinoids in regulating tumor cell growth and apoptosis and ongoing research is addressed to further dissect the precise mechanisms of cannabinoid antitumor action. However, endocannabinoids are now emerging as suppressors of angiogenesis and tumor spreading since they have been reported to inhibit angiogenesis, cell migration and metastasis in different types of cancer, pointing to a potential role of the endocannabinoid system as a target for a therapeutic approach of such malignant diseases. The potential use of cannabinoids to retard tumor growth and spreading is even more appealing considering that they show a good safety profile, regarding toxicity, and are already used in cancer patients as palliatives to stimulate appetite and to prevent devastating effects such as nausea, vomiting and pain.

<http://www.ncbi.nlm.nih.gov/pubmed/17342320>

<http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/is-cannabis-treatment-brain-tumours>

<http://www.ncbi.nlm.nih.gov/pubmed/22491047>

Abstract

Cannabinoids are a class of pharmacologic compounds that offer potential applications as antitumor drugs, based on the ability of some members of this class to limit inflammation, cell proliferation, and cell survival. In particular, emerging evidence suggests that agonists of cannabinoid receptors expressed by tumor cells may offer a novel strategy to treat cancer. Here, we review recent work that raises interest in the development and exploration of potent, nontoxic, and nonhabit forming cannabinoids for cancer therapy. [Cancer Res 2008;68(2):339–42]

<http://cancerres.aacrjournals.org/content/68/2/339>

The Cannabinoid WIN 55,212-2 Decreases Specificity Protein Transcription Factors and the Oncogenic Cap Protein eIF4E in Colon Cancer Cells

<http://mct.aacrjournals.org/content/12/11/2483.abstract>

Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents

<http://carcin.oxfordjournals.org/content/34/1/48.abstract>

Betulinic Acid Targets YY1 and ErbB2 through Cannabinoid Receptor-Dependent Disruption of MicroRNA-27a:ZBTB10 in Breast Cancer <http://ar.iiarjournals.org/content/31/11/3799.abstract>

Cannabinoid Receptor Agonist as an Alternative Drug in 5-Fluorouracil-resistant Gastric Cancer Cells

"These results indicate that a cannabinoid agonist may, indeed, be an alternative chemotherapeutic agent for 5-FU-resistant gastric cancer."

<http://ar.iiarjournals.org/content/33/6/2541.abstract>

A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma

"Glioblastoma multiforme (GBM) is highly resistant to current anticancer treatments, which makes it crucial to find new therapeutic strategies aimed at improving the poor prognosis of patients suffering from this disease. Δ^9 -Tetrahydrocannabinol (THC), the major active ingredient of marijuana, and other cannabinoid receptor agonists inhibit tumor growth in animal models of cancer, including glioma, an effect that relies, at least in part, on the stimulation of autophagy-mediated apoptosis in tumor cells. Here, we show that the combined administration of THC and temozolomide (TMZ; the benchmark agent for the management of GBM) exerts a strong antitumoral action in glioma xenografts, an effect that is also observed in tumors that are resistant to TMZ treatment."

<http://mct.aacrjournals.org/content/10/1/90.abstract>

Cannabinoid Receptors, CB1 and CB2, as Novel Targets for Inhibition of Non-Small Cell Lung Cancer Growth and Metastasis

Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths worldwide; however, only limited therapeutic treatments are available. Hence, we investigated the role of cannabinoid receptors, CB1 and CB2, as novel therapeutic targets against NSCLC.

<http://cancerpreventionresearch.aacrjournals.org/content/4/1/65.abstract>

Potential of Cannabinoid-Induced Cytotoxicity in Mantle Cell Lymphoma through Modulation of Ceramide Metabolism

"Our findings suggest that R-MA induces cell death in MCL via CB1-mediated up-regulation of the de novo ceramide synthesis pathway. Furthermore, this is the first study where the cytotoxic effect of a cannabinoid is enhanced by modulation of ceramide metabolism."

Cannabinoid Receptor Activation Induces Apoptosis through Tumor Necrosis Factor α -Mediated Ceramide De novo Synthesis in Colon Cancer Cells

Purpose: Cannabinoids have been recently proposed as a new family of potential antitumor agents. The present study was undertaken to investigate the expression of the two cannabinoid receptors, CB1 and CB2, in colorectal cancer and to provide new insight into the molecular pathways underlying the apoptotic activity induced by their activation

Conclusions: The present study shows that either CB1 or CB2 receptor activation induces apoptosis through ceramide de novo synthesis in colon cancer cells. Our data unveiled, for the first time, that TNF- α acts as a link between cannabinoid receptor activation and ceramide production.

<http://mcr.aacrjournals.org/content/7/7/1086.abstract>

Here we review the relationship between the endocannabinoid system and anti-tumor actions (inhibition of cell proliferation and migration, induction of apoptosis, reduction of tumor growth) of the cannabinoids in different types of cancer. This review will focus on examining how activation of the endocannabinoid system impacts breast, prostate and bone cancers in both in vitro and in vivo systems. The therapeutic potential of cannabinoids for cancer, as identified in clinical trials, is also discussed. Identification of safe and effective treatments to manage and improve cancer therapy is critical to improve quality of life and reduce unnecessary suffering in cancer patients. In this regard, cannabis-like compounds offer therapeutic potential for the treatment of breast, prostate and bone cancer in patients. Further basic research on anti-cancer properties of cannabinoids as well as clinical trials of cannabinoid therapeutic efficacy in breast, prostate and bone cancer is therefore warranted.

<http://onlinelibrary.wiley.com/doi/10.1111/j.1476-5381.2011.01327.x/abstract>

Regulation of circulating endocannabinoids associated with cancer and metastases in mice and humans.

<http://www.ncbi.nlm.nih.gov/pubmed/25594019>

Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychoactive cannabinoid

<http://carcin.oxfordjournals.org/content/35/12/2787.abstract>

The antitumor action of cannabinoids on glioma tumorigenesis.

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.

<http://www.ncbi.nlm.nih.gov/pubmed/25472761>

Regulation of inflammation and proliferation of human bladder carcinoma cells by type-1 and type-2 cannabinoid receptors. <http://www.ncbi.nlm.nih.gov/pubmed/25445433>

Abstract

Cannabinoids are a class of chemical compounds with a wide spectrum of pharmacological effects, mediated by two specific plasma membrane receptors (CB1 and CB2). Recently, CB1 and CB2 expression levels have been detected in human tumors, including those of brain. Cannabinoids-endocannabinoids exert anti-inflammatory, anti-proliferative, anti-invasive, anti-metastatic and pro-apoptotic effects in different cancer types, both in vitro and in vivo in animal models, after local or systemic administration. We present the available experimental and clinical data, to date, regarding the antitumor action of cannabinoids on the tumorigenesis of gliomas.

<http://www.ncbi.nlm.nih.gov/pubmed/25472761>

Critical Reviews in Oncology/Hematology 83 (2012) 1–10

The intersection between cannabis and cancer in the United States

Conclusions

Interest in and use of medicinal cannabis and cannabinoids have risen dramatically in the last 30 years as synthetic and purified cannabinoids have entered the market and states have passed laws eliminating criminal penalties for cannabis possession, use, or physician recommendation for approved medical purposes. Medical cannabis remains a paradox in many ways. Cannabis smoke may be carcinogenic but it has been difficult to conclusively link cannabis use and cancer development epidemiologically, and cannabinoids have shown some promise as anti-cancer therapies. Cannabinoids can palliate some cancer symptoms but it is unclear how effective they are compared to or combined with conventional therapies, or even whether cannabis, purified cannabinoids, or synthetic cannabinoids are more effective. Moreover, while 15 states and the District of Columbia have eliminated criminal penalties for medical cannabis, it remains illegal on the federal level. New research into cannabinoids and cancer is needed, particularly with respect to cannabinoids' effects on the standard oncology outcomes of tumor growth and patient survival. The future interplay between cannabis and cancer in the US is uncertain and will be influenced by public sentiment and political persuasion, but the hope is that scientific inquiry will help guide the discussion by providing further insight into the potential risks and benefits of cannabis and cannabinoids in cancer development, treatment, and palliation.

[http://www.croh-online.com/article/S1040-8428\(11\)00231-9/pdf](http://www.croh-online.com/article/S1040-8428(11)00231-9/pdf)

Medical Marijuana May Treat Aggressive Forms Of Breast Cancer

<http://www.medicaljane.com/2013/10/17/study-cannabis-may-treat-aggressive-forms-of-breast-cancer/>

Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition

Background

ErbB2-positive breast cancer is characterized by highly aggressive phenotypes and reduced responsiveness to standard therapies. Although specific ErbB2-targeted therapies have been designed, only a small percentage of patients respond to these treatments and most of them eventually relapse. The existence of this population of particularly aggressive and non-responding or relapsing patients urges the search for novel therapies. The purpose of this study was to determine whether cannabinoids might constitute a new therapeutic tool for the treatment of ErbB2-positive breast tumors. We analyzed their antitumor potential in a well-established and clinically relevant model of ErbB2-driven metastatic breast cancer: the MMTV-neu mouse. We also analyzed the expression of cannabinoid targets in a series of 87 human breast tumors.

Results

Our results show that both Δ^9 -tetrahydrocannabinol, the most abundant and potent cannabinoid in marijuana, and JWH-133, a non-psychotropic CB2 receptor-selective agonist, reduce tumor growth, tumor number, and the amount/severity of lung metastases in MMTV-neu mice. Histological analyses of the tumors revealed that cannabinoids inhibit cancer cell proliferation, induce cancer cell apoptosis, and impair tumor angiogenesis. Cannabinoid antitumoral action relies, at least partially, on the inhibition of the pro-tumorigenic Akt pathway. We also found that 91% of ErbB2-positive tumors express the non-psychotropic cannabinoid receptor CB2.

Conclusions

Taken together, these results provide a strong preclinical evidence for the use of cannabinoid-based therapies for the management of ErbB2-positive breast cancer.

<http://www.molecular-cancer.com/content/9/1/196#B4>

<http://www.medicaljane.com/2013/07/27/study-shows-cannabinoids-inhibit-tumor-growth/>

FEDERAL GOVERNMENT CANNABIS AND CANCER RESEARCH- All Remaining Cancer Info Listed Below is from FEDERAL GOVERNMENT NCI, NIH

About PDQ

Physician Data Query (PDQ) is the National Cancer Institute's (NCI's) comprehensive cancer information database. The PDQ database contains summaries of the latest published information on cancer prevention, detection, genetics, treatment, supportive care, and complementary and alternative medicine. Most summaries come in two versions. The health professional versions

have detailed information written in technical language. The patient versions are written in easy-to-understand, nontechnical language. Both versions have cancer information that is accurate and up to date and most versions are also available in [Spanish](#).

PDQ is a service of the NCI. The NCI is part of the National Institutes of Health (NIH). NIH is the federal government's center of biomedical research. The PDQ summaries are based on an independent review of the medical literature. They are not policy statements of the NCI or the NIH.

Purpose of This Summary

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.

Reviewers and Updates

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 Cancer Complementary and Alternative Medicine Editorial Board](#).

"The use of *Cannabis* for medicinal purposes dates back to ancient times"

"*Cannabis* has been shown to kill cancer cells in the laboratory"

<http://www.cancer.gov/cancertopics/pdq/cam/cannabis/patient>

"What is the history of the medical use of *Cannabis*?"

The use of *Cannabis* for medicinal purposes dates back at least 3,000 years. It came into use in Western in the 19th century and was said to relieve pain, inflammation, spasms, and convulsions.

In 1937, the U.S. Treasury began taxing *Cannabis* under the Marijuana Tax Act at one dollar per ounce for medicinal use and one hundred dollars per ounce for recreational use. The American Medical Association (AMA) opposed this regulation of *Cannabis* and did not want studies of its potential medicinal benefits to be limited. In 1942, *Cannabis* was removed from the

U.S. Pharmacopoeia because of continuing concerns about its safety. In 1951, Congress passed the Boggs Act, which included *Cannabis* with narcotic drugs for the first time.

Under the Controlled Substances Act of 1970, marijuana was classified as a Schedule I drug. Other Schedule I drugs include heroin, LSD, mescaline, methaqualone, and gamma-hydroxybutyrate (GHB).

Although *Cannabis* was not believed to have any medicinal use, the U.S. government distributed it to patients on a case-by-case basis under the Compassionate Use Investigational New Drug (IND) program between 1978 and 1992.

In the past 20 years, researchers have studied how cannabinoids act on the brain and other parts of the body. Cannabinoid receptors (molecules that bind cannabinoids) have been discovered in brain cells and nerve cells in other parts of the body. The presence of cannabinoid receptors on immune system cells suggests that cannabinoids may have a role in immunity”

1. What are cannabinoids?

Cannabinoids are active chemicals in *Cannabis* that cause drug-like effects throughout the body, including the central nervous system and the immune system. They are also known as phytocannabinoids. The main active cannabinoid in *Cannabis* is delta-9-THC. Another active cannabinoid is cannabidiol (CBD), which may relieve pain and lower inflammation without causing the "high" of delta-9-THC.

Cannabinoids may be useful in treating the side effects of cancer and cancer treatment.

Other possible effects of cannabinoids include:

- Anti-inflammatory activity.
 - Blocking cell growth.
 - Preventing the growth of blood vessels that supply tumors.
 - Antiviral activity.
 - Relieving muscle spasms caused by multiple sclerosis.
- ### 2. Have any preclinical (laboratory or animal) studies been conducted using *Cannabis* or cannabinoids?

Preclinical studies of cannabinoids have investigated the following activities:

Antitumor activity

- Studies in mice and rats have shown that cannabinoids may inhibit tumor growth by causing cell death, blocking cell growth, and blocking the development of blood vessels needed by tumors to grow. Laboratory and animal studies have shown that cannabinoids may be able to kill cancer cells while protecting normal cells.

- A study in mice showed that cannabinoids may protect against inflammation of the colon and may have potential in reducing the risk of colon cancer, and possibly in its treatment.
- A laboratory study of delta-9-THC in hepatocellular carcinoma (liver cancer) cells showed that it damaged or killed the cancer cells. The same study of delta-9-THC in mouse models of liver cancer showed that it had antitumor effects. Delta-9-THC has been shown to cause these effects by acting on molecules that may also be found in non-small cell lung cancer cells and breast cancer cells.
- A laboratory study of cannabidiol (CBD) in estrogen receptor positive and estrogen receptor negative breast cancer cells showed that it caused cancer cell death while having little effect on normal breast cells. Studies in mouse models of metastatic breast cancer showed that cannabinoids may lessen the growth, number, and spread of tumors.
- A laboratory study of cannabidiol (CBD) in human glioma cells showed that when given along with chemotherapy, CBD may make chemotherapy more effective and increase cancer cell death without harming normal cells. Studies in mouse models of cancer showed that CBD together with delta-9-THC may make chemotherapy such as astemizole more effective.

Stimulating appetite

- Many animal studies have shown that delta-9-THC and other cannabinoids stimulate appetite and can increase food intake.

Pain relief

- Cannabinoid receptors (molecules that bind cannabinoids) have been studied in the brain, spinal, and nerve endings throughout the body to understand their roles in pain relief.
- Cannabinoids have been studied for anti-inflammatory effects that may play a role in pain relief.

3. Have any clinical trials (research studies with people) of *Cannabis* or cannabinoid use by cancer patients been conducted?

No clinical trials of *Cannabis* as a treatment for cancer in humans have been found in the [CAM on PubMed](#) database maintained by the [National Institutes of Health](#).

Cannabis and cannabinoids have been studied in clinical trials for ways to manage side effects of cancer and cancer therapies, including the following:

Nausea and vomiting

- Delta-9-THC taken by mouth: Two cannabinoid drugs approved in the United States are available under the names dronabinol and nabilone. Both dronabinol and nabilone are approved by the [Food and Drug Administration](#) (FDA) for the treatment

of chemotherapy-related nausea and vomiting in patients who have not responded to standard therapy. Many clinical trials have shown that both dronabinol and nabilone worked as well as or better than some of the weaker FDA-approved drugs to relieve nausea and vomiting. Newer drugs given for chemotherapy-related nausea have not been directly compared with *Cannabis* or cannabinoids in cancer patients.

- Inhaled *Cannabis*: Three small trials have studied inhaled *Cannabis* for the treatment of chemotherapy-related nausea and vomiting. Various study methods and chemotherapy agents were used with mixed results. There is not enough information to interpret these findings.

Stimulating appetite

- Delta-9-THC taken by mouth: A clinical trial compared delta-9-THC (dronabinol) and a standard drug (megestrol) in patients with advanced cancer and loss of appetite. Results showed that delta-9-THC was not as effective in increasing appetite or weight gain in advanced cancer patients compared with standard therapy. However, a clinical trial of patients with HIV /AIDS and weight loss found that those who took delta-9-THC had increased appetite and stopped losing weight compared with patients who took a placebo.
- Inhaled *Cannabis*: There are no published studies of the effect of inhaled *Cannabis* on cancer patients with loss of appetite. Studies of healthy people who inhaled *Cannabis* showed that they consumed more calories, especially high-fat and sweet snacks.

Pain relief

- Combining cannabinoids with opioids: In a small study of 21 patients with chronic pain, combining vaporized *Cannabis* with morphine relieved pain better than morphine alone, while combining vaporized *Cannabis* with oxycodone did not produce significantly greater pain relief. These findings should be tested in further studies.
- Delta-9-THC taken by mouth: Two small clinical trials of oral delta-9-THC showed that it relieved cancer pain. In the first study, patients had good pain relief as well as relief of nausea and vomiting and better appetite. A second study showed that delta-9-THC could be given in doses that gave pain relief comparable to codeine. An observational study of nabilone also showed that it relieved cancer pain along with nausea, anxiety, and distress when compared with no treatment. Neither dronabinol nor nabilone is approved by the FDA for pain management.
- Whole *Cannabis* plant extract medicine: A study of a whole-plant extract of *Cannabis* that contained specific amounts of cannabinoids, which was sprayed under the tongue, found it was effective in patients with advanced cancer whose pain was not relieved by strong opioids alone. Patients who received the lower doses of cannabinoid spray showed markedly better pain control and less sleep loss compared with patients who received a placebo. Results showed that, for some

patients, control of their cancer-related pain continued without needing higher doses of spray or higher doses of their other pain medicines.

Anxiety and sleep

- Inhaled *Cannabis*: A small case series found that patients who inhaled marijuana had improved mood, improved sense of well-being, and less anxiety.
- Whole *Cannabis* plant extract spray: A trial of a whole-plant extract of *Cannabis* that contained specific amounts of cannabinoids, which was sprayed under the tongue, found that patients had improved sleep quality.

4. Have any side effects or risks been reported from *Cannabis* and cannabinoids?

Adverse side effects of cannabinoids may include:

- Rapid beating of the heart.
- Low blood pressure.
- Muscle relaxation.
- Bloodshot eyes.
- Slowed digestion and movement of food by the stomach and intestines.
- Dizziness.
- Depression.
- Hallucinations.
- Paranoia.

Because *Cannabis* smoke contains many of the same substances as tobacco smoke, there are concerns about how inhaled cannabis affects the lungs. A study of over 5,000 men and women without cancer over a period of 20 years found that smoking tobacco was linked with some loss of lung function but that occasional and low use of cannabis was not linked with loss of lung function.

Because use of *Cannabis* over a long time may have harmful effects on the endocrine and reproductive, rates of testicular germ cell tumors (TGCTs) in *Cannabis* users have been studied. Larger studies that follow patients over time and laboratory studies of cannabinoid receptors in TGCTs are needed to find if there is a link between *Cannabis* use and a higher risk of TGCTs.

Both *Cannabis* and cannabinoids may be addictive.

Symptoms of withdrawal from cannabinoids may include:

- Irritability.
- Trouble sleeping.

- Restlessness.
- Hot flashes.
- Nausea and cramping (rarely occur).

These symptoms are mild compared to withdrawal from opiates and usually lessen after a few days.

5. **Are *Cannabis* or cannabinoids approved by the U.S. Food and Drug Administration for use as a cancer treatment in the United States?**

The U.S. Food and Drug Administration has not approved *Cannabis* or cannabinoids for use as a cancer treatment.

6. **Are *Cannabis* or cannabinoids approved by the U.S. Food and Drug Administration for use as a treatment for cancer-related symptoms or side effects of cancer therapy?**

Cannabis is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of any cancer-related symptom or side effect of cancer therapy.

Two cannabinoids (dronabinol and nabilone) are approved by the FDA for the treatment of chemotherapy-related nausea and vomiting in patients who have not responded to standard therapy.

○

<http://www.cancer.gov/cancertopics/pdq/cam/cannabis/patient/page2>

A spokeswoman for the Royal Free Hospital confirmed Mr. Cutler had not received any cancer treatment since his transplant in November 2009. Read more: <http://www.dailymail.co.uk/health/article-2699875/1-cured-cancer-CANNABIS-OIL.html#ixzz3P9UcPyYk>

Tourette Syndrome

Cannabinoids reduce symptoms of Tourette's syndrome.

Abstract

Currently, the treatment of Tourette's syndrome (TS) is unsatisfactory. Therefore, there is expanding interest in new therapeutical strategies. Anecdotal reports suggested that the use of cannabis might improve not only tics, but also behavioral problems in patients with TS. A single-dose, cross-over study in 12 patients, as well as a 6-week, randomized trial in 24 patients, demonstrated that Delta9-tetrahydrocannabinol (THC), the most psychoactive ingredient of cannabis, reduces tics in TS patients. No serious adverse effects occurred and no impairment on neuropsychological performance was observed. If well-established drugs either fail to improve tics or cause significant adverse effects, in

adult patients, therapy with Delta9-THC should be tried. At present, it remains unclear whether herbal cannabis, different natural or synthetic cannabinoid CB1-receptor agonists or agents that interfere with the inactivation of endocannabinoids, may have the best adverse effect profile in TS

<http://www.ncbi.nlm.nih.gov/pubmed/14521482>

A clinical study conducted at the Medical School of Hannover (Germany) and published in the current issue of Pharmacopsychiatry demonstrated that a single dose of THC reduces symptoms of Tourette-Syndrome.

Under the guidance of Dr. Kirsten Mueller-Vahl 12 adult TS patients received THC (5, 7.5 or 10 mg) in a double-blind placebo-controlled crossover design. Patients received either a single dose of oral THC first or placebo first on two days separated by 4 weeks before they were crossed over to receive the other treatment.

THC resulted in a significant improvement of symptoms. At the end of the study nine patients assessed the THC treatment day overall more positive than the placebo day. Three patients experienced the placebo day more positive. No serious adverse reactions occurred. Blood pressure and pulse did not change significantly. Five patients experienced mild adverse reactions, lasting 1 to 6 hours. There was a significant correlation between tic improvement and maximum blood plasma concentration of 11-OH-THC.

Gilles de la Tourette-Syndrome (Tourette-Syndrome, TS) is a complex neurological disorder characterized by multiple motor tics (sudden movements) and one or more vocal tics. Another six-week-study with 24 patients that has been completed in the meantime confirmed the results of this earlier study.

(Sources: Mueller-Vahl K, et al. Treatment of Tourette-Syndrome with delta-9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry, April 2002. Personal communication of Kirsten Mueller-Vahl)

Heart Disease

An ultra-low dose of tetrahydrocannabinol provides cardio protection

CONCLUSION:

A single ultra-low dose of THC before ischemia is a safe and effective treatment that reduces myocardial ischemic damage.

<http://www.ncbi.nlm.nih.gov/pubmed/23537701>

THC Has The Upper Hand On Cardiac Damage

<http://www.medicaljane.com/2013/07/22/thc-is-beneficial-for-brain-heart-health/>

Abstract

The role of the endocannabinoid system in nicotine addiction is being increasingly acknowledged. We conducted a pilot, randomized double blind placebo controlled study set out to assess the impact of the ad-hoc use of cannabidiol (CBD) in smokers who wished to stop smoking. 24 smokers were randomized to receive an inhaler of CBD (n = 12) or placebo (n = 12) for one week, they were instructed to use the inhaler when they felt the urge to smoke. Over the treatment week, placebo treated smokers showed no differences in number of cigarettes smoked. In contrast, those treated with CBD significantly reduced the number of cigarettes smoked by ~ 40% during treatment. Results

also indicated some maintenance of this effect at follow-up. These preliminary data, combined with the strong preclinical rationale for use of this compound, suggest CBD to be a potential treatment for nicotine addiction that warrants further exploration.

<http://www.sciencedirect.com/science/article/pii/S030646031300083X>

<http://www.medicaljane.com/2013/10/25/study-cannabidiol-cbd-may-reduce-cigarette-consumption/>

Chronic Pain

Physician's Organization in Canada Releases Guidelines for Prescribing Medical Cannabis for Pain

Overall, the guidelines provided by the College of Family Physicians of Canada are well-informed, evidence-based, reasonable, and progressive. While some may find that the guidelines attempt to put too many limitations on medicinal cannabis use, safety considerations, appropriately, seem to be at the forefront of their creation. Potential improvements to the guidelines could include (1) recommendations for diseases/symptoms, other than neuropathic pain, that may be benefited by medical cannabis use, and (2) discussion of additional methods of delivery, including vaporization and ingestion, which would be useful for all practitioners, but especially for those who are uncomfortable recommending their patients smoke.

The introduction of reasonable guidelines surrounding medical cannabis use by established physician's organizations, in Canada and worldwide, will likely help to decrease the stigma associated with/increase knowledge about medical cannabis use, especially for older and more conservative patients and physicians, thereby increasing access to this relatively safe treatment option for those in need.

<http://www.medicaljane.com/2014/12/31/physicians-organization-in-canada-releases-guidelines-for-prescribing-medical-cannabis-for-pain/>

Prescribing smoked cannabis for chronic noncancer pain

Preliminary recommendations

This review offers preliminary guidance on the indications, contraindications, and dosing of smoked cannabis in the treatment of chronic noncancer pain, pending the development of formal guidelines. Pain is the most common reason for using medical cannabis.

<http://www.cfp.ca/content/60/12/1083.long>

<http://www.medicaljane.com/2014/12/31/study-study-whole-plant-cannabis-as-add-on-therapy-for-chronic-non-cancer-pain/>

Marijuana for Painful Peripheral Neuropathy?

Judith Feinberg, MD reviewing Abrams DI et al. Neurology 2007 Feb 13.

Despite relatively low concentrations of active cannabinoids, the marijuana cigarettes used in this study reduced chronic pain associated with peripheral neuropathy and also alleviated acute pain. The level of pain relief was comparable to, or better than, that seen with other drugs, such as anticonvulsants and tricyclic antidepressants, that have been evaluated for peripheral neuropathy. Legal issues with the medical use of marijuana abound, but I think that clinicians and patients who are comfortable with the concept of therapeutic cannabis use can explore its usefulness in ameliorating painful peripheral neuropathy, especially in situations in which other approaches have failed.

<http://www.jwatch.org/ac200704300000001/2007/04/30/marijuana-painful-peripheral-neuropathy>

Cannabinoids for chronic pain

<http://www.bmj.com/content/336/7637/167>

More evidence cannabis can help in neuropathic pain

Henry J. McQuay DM

Key points

- Current treatments do not help all patients with neuropathic pain.
- Cannabis can produce moderate analgesia in patients with neuropathic pain.
- This analgesic effect may be more pronounced in central, as opposed to peripheral, neuropathic pain.

<http://www.cmaj.ca/content/182/14/1494.full.pdf+html>

Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Conclusion: A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated. Further long-term safety and efficacy studies are indicated. (International Standard Randomized Controlled Trial Register no. ISRCTN68314063)

<http://www.cmaj.ca/content/182/14/E694.abstract>

Dynamic changes to the endocannabinoid system in models of chronic pain

The evidence that spinal CB2 receptors have a novel role in the modulation of nociceptive processing in models of neuropathic pain, as well as in models of cancer pain and arthritis is discussed. Recent advances in our understanding of the spinal location of the key enzymes that regulate the levels of the

endocannabinoid 2-AG are discussed alongside the outcomes of recent studies of the effects of inhibiting the catabolism of 2-AG in models of pain.

<http://rstb.royalsocietypublishing.org/content/367/1607/3300.abstract>

HIV

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

Conclusion: Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

<http://www.neurology.org/content/68/7/515.abstract>

Stress and Anxiety: PTSD, Psychiatric Stress Disorders. Mental Health

Affecting 12% of Americans in their lifetime, Social Anxiety Disorder (SAD) is the most common form of anxiety and one of the most psychiatric disorders in general. It is also referred to as social phobia.

By definition, Social Anxiety Disorder is characterized by intense fear in one or more social situations. In turn, this fear can cause distress to the point that it impairs daily functioning.

Interestingly enough, people who suffer from SAD experience anxiety that can be triggered by “perceived or actual scrutiny” from others. For some this only happens in specific situations, but others may have to deal with this anxiety constantly.

<http://www.medicaljane.com/2014/05/28/study-cannabidiol-cbd-may-help-treat-social-anxiety-disorder/>

Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report.

Abstract

Animal and human studies indicate that cannabidiol (CBD), a major constituent of cannabis, has anxiolytic properties. However, no study to date has investigated the effects of this compound on human pathological anxiety and its underlying brain mechanisms. The aim of the present study was to investigate this in patients with generalized social anxiety disorder (SAD) using functional neuroimaging. Regional cerebral blood flow (rCBF) at rest was measured twice using (99m)Tc-ECD SPECT in 10 treatment-naïve patients with SAD. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. 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. Relative to placebo, CBD was associated with significantly decreased subjective anxiety ($p < 0.001$), reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus ($p < 0.001$, uncorrected), and increased ECD uptake in the right posterior cingulate gyrus ($p < 0.001$,

uncorrected). These results suggest that CBD reduces anxiety in SAD and that this is related to its effects on activity in limbic and paralimbic brain areas.

<http://www.ncbi.nlm.nih.gov/pubmed/20829306>

<http://www.medicaljane.com/2013/07/19/cbd-gives-birth-to-new-neurons-in-the-brain-2/>

The International Journal of Neuropsychopharmacology

The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system

Abstract

Cannabidiol (CBD), the main non-psychotomimetic component of the plant *Cannabis sativa*, exerts therapeutically promising effects on human mental health such as inhibition of psychosis, anxiety and depression. However, the mechanistic bases of CBD action are unclear. Here we investigate the potential involvement of hippocampal neurogenesis in the anxiolytic effect of CBD in mice subjected to 14 d chronic unpredictable stress (CUS).

...

These findings support that the anxiolytic effect of chronic CBD administration in stressed mice depends on its proneurogenic action in the adult hippocampus by facilitating endocannabinoid-mediated signaling.

<http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8930251&fulltextType=R&fileId=S1461145712001502>

CBD has shown promise in preventing cancer from cigarette smoke, reducing heart damage from chemotherapy, and many more studies are being conducted.

CBD inhibits the uptake of anandamide, allowing it to stay in the blood stream longer.

One specific area of research has focused on cannabidiol's interaction with anandamide. Anandamide is an endocannabinoid, which means our body produces it naturally. It effects the CB1 receptors, as well as the CB2 receptors, and has been found to fight against human breast cancer.

Some research has also found that anandamide could play a role in the psychotic symptoms of schizophrenia. According to this study, anandamide is inversely correlated with psychotic symptoms; high levels of anandamide seems to reduce psychosis in patients.

<http://www.medicaljane.com/2013/08/30/cannabidiol-cbd-may-reduce-psychotic-symptoms-of-schizophrenia/>

Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms.

Abstract

The endocannabinoids are a family of bioactive lipids that activate CB1 cannabinoid receptors in the brain and exert intense emotional and cognitive effects. Here, we have examined the role of

endocannabinoid signaling in psychotic states by measuring levels of the endocannabinoid anandamide in cerebrospinal fluid (CSF) of acute paranoid-type schizophrenic patients. We found that CSF anandamide levels are eight-fold higher in antipsychotic-naïve first-episode paranoid schizophrenics ($n = 47$) than healthy controls ($n = 84$), dementia patients ($n = 13$) or affective disorder patients ($n = 22$). Such an alteration is absent in schizophrenics treated with 'typical' antipsychotics ($n = 37$), which antagonize dopamine D2-like receptors, but not in those treated with 'atypical' antipsychotics ($n = 34$), which preferentially antagonize 5HT(2A) receptors. Furthermore, we found that, in nonmedicated acute schizophrenics, CSF anandamide is negatively correlated with psychotic symptoms ($rS = -0.452$, $P = 0.001$). The results suggest that anandamide elevation in acute paranoid schizophrenia may reflect a compensatory adaptation to the disease state.

<http://www.ncbi.nlm.nih.gov/pubmed/15354183?dopt=Abstract&holding=npg>

<http://www.medicaljane.com/2014/08/11/study-cannabinoid-therapies-may-help-treat-stress-induced-anxiety-disorders/>

Central anandamide deficiency predicts stress-induced anxiety: behavioral reversal through endocannabinoid augmentation

Stress is a major risk factor for the development of mood and anxiety disorders; elucidation of novel approaches to mitigate the deleterious effects of stress could have broad clinical applications. Pharmacological augmentation of central endogenous cannabinoid (eCB) signaling may be an effective therapeutic strategy to mitigate the adverse behavioral and physiological consequences of stress. Here we show that acute foot-shock stress induces a transient anxiety state measured 24 h later using the light–dark box assay and novelty-induced hypophagia test. Acute pharmacological inhibition of the anandamide-degrading enzyme, fatty acid amide hydrolase (FAAH), reverses the stress-induced anxiety state in a cannabinoid receptor-dependent manner. FAAH inhibition does not significantly affect anxiety-like behaviors in non-stressed mice. Moreover, whole brain anandamide levels are reduced 24 h after acute foot-shock stress and are negatively correlated with anxiety-like behavioral measures in the light–dark box test. These data indicate that central anandamide levels predict acute stress-induced anxiety, and that reversal of stress induced anandamide deficiency is a key mechanism subserving the therapeutic effects of FAAH inhibition. These studies provide further support that eCB-augmentation is a viable pharmacological strategy for the treatment of stress-related neuropsychiatric disorders.

Translational Psychiatry (2014) 4, e408; doi:10.1038/tp.2014.53; published online 8 July 2014

<http://cannabisclinicians.org/wp-content/uploads/2014/07/Stress-Induced-Anxiety-2014.pdf>

Cannabinoids ameliorate impairments induced by chronic stress to synaptic plasticity and short-term memory.

Our findings suggest that cannabinoid receptor activation could represent a novel approach to the treatment of cognitive deficits that accompany a variety of stress-related neuropsychiatric disorders

<http://www.ncbi.nlm.nih.gov/pubmed/23426383>

Cannabinoids prevent the development of behavioral and endocrine alterations in a rat model of intense stress.

Cannabinoids have recently emerged as a possible treatment of stress- and anxiety-related disorders such as post-traumatic stress disorder (PTSD). Here, we examined whether cannabinoid receptor

activation could prevent the effects of traumatic stress on the development of behavioral and neuroendocrine measures in a rat model of PTSD, the single-prolonged stress (SPS) model....

These findings suggest that (i) there may be an optimal time window for intervention treatment with cannabinoids after exposure to a highly stressful event, (ii) some of the preventive effects induced by WIN are mediated by an activation of CB1 receptors in the BLA, and (iii) cannabinoids could serve as a pharmacological treatment of stress- and trauma-related disorders.

<http://www.ncbi.nlm.nih.gov/pubmed/21918506>

<http://www.medicaljane.com/2013/07/31/chronic-stress-effects-memory-learning-recent-study-shows-cannabis-can-help/>

Cannabinoids and traumatic stress modulation of contextual fear extinction and GR expression in the amygdala-hippocampal-prefrontal circuit.

Abstract

Considerable evidence suggests that cannabinoids modulate the behavioral and physiological response to stressful events. We have recently shown that activating the cannabinoid system using the CB1/CB2 receptor agonist WIN55,212-2 (WIN) in proximity to exposure to single-prolonged stress (SPS), a rat model of emotional trauma, prevented the stress-induced enhancement of acoustic startle response, the impairment in avoidance extinction and the enhanced negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis (Ganon-Elazar and Akirav, 2012). Some of the effects were found to be mediated by CB1 receptors in the basolateral amygdala (BLA). Here we examined whether cannabinoid receptor activation in a putative brain circuit that includes the BLA, hippocampus and prefrontal cortex (PFC), could prevent the effects of traumatic stress on contextual fear extinction and alterations in glucocorticoid receptor (GR) protein levels. We found that: (i) SPS impaired contextual fear extinction tested one week after trauma exposure and that WIN prevented the stress-induced impairment of extinction when microinjected immediately after trauma exposure into the BLA or hippocampus (5 µg), but not when microinjected into the PFC, (ii) the ameliorating effects of WIN on contextual extinction were prevented by blocking GRs in the BLA and hippocampus, and (iii) SPS up regulated GRs in the BLA, PFC and hippocampus and systemic WIN administration (0.5 mg/kg) after trauma exposure normalized GR levels in the BLA and hippocampus, but not in the PFC. Cannabinoid receptor activation in the aftermath of trauma exposure may regulate the emotional response to the trauma and prevent stress-induced impairment of extinction and GR up regulation through the mediation of CB1 receptors in the BLA and hippocampus. **Taken together, the findings suggest that the interaction between the cannabinoid and glucocorticoid systems is crucial in the modulation of emotional trauma.**

<http://www.ncbi.nlm.nih.gov/pubmed/23433741>

Cannabinoid receptor activation prevents the effects of chronic mild stress on emotional learning and LTP in a rat model of depression.

Abstract

Most psychiatric disorders are characterized by emotional memory or learning disturbances. Chronic mild stress (CMS) is a common animal model for stress-induced depression. Here we examined whether 3 days of treatment using the CB1/2 receptor agonist WIN55,212-2 could ameliorate the effects of CMS on emotional learning (ie, conditioned avoidance and extinction), long-term potentiation (LTP) in the hippocampal-accumbens pathway, and depression-like symptoms (ie, coping with stress behavior,

anhedonia, and weight changes). ...**The findings suggest that enhancing cannabinoid signaling could represent a novel approach to the treatment of cognitive deficits that accompany stress-related depression.**

<http://www.ncbi.nlm.nih.gov/pubmed/24141570>

Anandamide May Postpone The Onset Of Psychosis

Risk Syndrome for First Psychosis is understood as the beginnings of schizophrenia. Despite hallucinations or delusions, one is still able to identify with reality.

Not only does the cannabinoid system seem to help reduce psychotic symptoms, but it also may postpone the onset of psychosis. In regards to psychosis, there is a period of time prior to the full onset of symptoms called the prodrome.

Actually, there is a completely new psychiatric diagnosis for this period in the new version of the Diagnostic and Statistic Manual of Mental Disorders (DSM): risk syndrome for first psychosis.

Research has suggested that anandamide may help fight off a complete psychotic break. When studied, high levels of anandamide were responsible for a longer prodrome period. It took longer for the risk syndrome for first psychosis to develop into schizophrenia.

<http://www.medicaljane.com/2013/08/30/cannabidiol-cbd-may-reduce-psychotic-symptoms-of-schizophrenia/>

Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

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.

<http://www.nature.com/tp/journal/v2/n3/full/tp201215a.html#bib19>

Cannabidiol (CBD) Vs Antipsychotics

Last year, an international team of researchers published a study in the journal Translational Psychiatry. They compared benefits of CBD and amisulpride, a potent antipsychotic, in 42 acute schizophrenia patients.

It makes sense that they chose amisulpride; most of the researchers are from Germany, where it is used to treat schizophrenia. In fact, it is used in many European countries (France, Germany, Italy, Switzerland, UK, etc.), Israel, New Zealand, and Australia, but it's not approved by the FDA in the US.

Side effects of amisulpride include nausea, weight gain, insomnia, anxiety, vomiting, and orgasmic dysfunction.

The researchers found that cannabidiol and amisulpride were both "safe and effective," but they declared CBD superior because it has "a better side-effect profile." The study also came to the conclusion that CBD increased the amount of anandamide, which was the reason for its success.

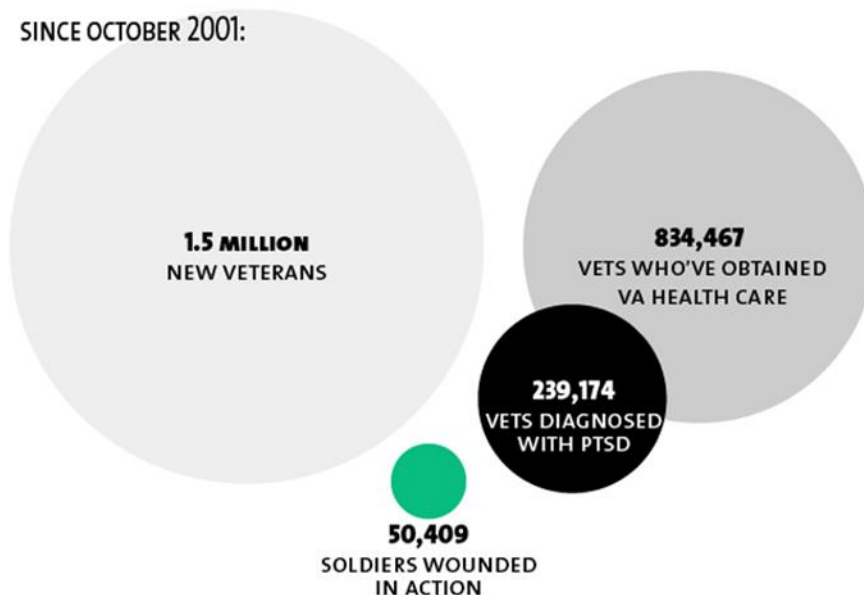
A significant amount of recent research has pointed towards a beneficial relationship between cannabidiol and anandamide. CBD seems to inhibit the deactivation of anandamide, which has been linked to human breast cancer and now, the psychotic symptoms of schizophrenia.

<http://www.medicaljane.com/2013/08/30/cannabidiol-cbd-may-reduce-psychotic-symptoms-of-schizophrenia/>

VETERANS, PTSD, CANNABIS and VA

PTSD IS FAR MORE COMMON THAN PHYSICAL WOUNDS

SINCE OCTOBER 2001:



SOURCES: DEPARTMENT OF VETERANS AFFAIRS, DEPARTMENT OF DEFENSE

Mother Jones

What is Post-traumatic Stress Disorder (PTSD)?

<http://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd/index.shtml#part4>

<http://www.medicaljane.com/ailment/ptsd/>

In 2010 the U.S. Department of Veterans Affairs formally began to allow the use of medical marijuana by veterans treated at its medical facilities in states where it is legal. That means that veterans no longer have to worry about losing benefits if they test positive for marijuana in those states.

Veterans and military troops transitioning back into civilian life are facing a number of disorders, and many are suffering severely. Post-traumatic stress disorder (PTSD) is an extremely severe anxiety disorder that many veterans develop after their psychological trauma they experienced while at war. It is a horrible disorder to endure and many veterans are currently being prescribed powerful addictive drugs to treat the symptoms.

These drugs work for some, but others become addicted and the drugs are affecting their lives. The prevalence of substance abuse among veterans has increased substantially and some are even committing suicide. For this reason exactly, veterans are turning to cannabis more and more to deal with the crippling symptoms of PTSD, traumatic brain injuries, and chronic pain.

In 2010, a national ABC News/Washington Post poll found that 81% of the country supports legalizing medical use, yet the government stubbornly denies access to the alternative medicine.

Subsequently, in **April of 2011 the FDA approved a clinical trial involving cannabis for treating PTSD.** However, the trial is in current legal limbo because the Health and Human Services Department is making it difficult for the non-profit group to get the government-grown marijuana. http://www.washingtonpost.com/national/health-science/marijuana-study-of-traumatized-veterans-stuck-in-regulatory-limbo/2011/09/30/glQAZfYLDL_story.html

With suicides outnumbering combat fatalities by a ratio of 25 to 1, and as much as 18% of Iraq veterans returning with PTSD, it would be negligent of the government to keep ignoring and delaying the issue.

Helpful Sources for Veterans, PTSD, and Medical Marijuana:

FOR HELP: call 1-800-273-8255 text: 838255 or visit www.veteranscrisisline.net to live chat.
<http://www.veteransformedicalmarijuana.org/pain-treatment>

Founded in 2014, Operation Grow4Vets is the only organization providing America's heroes with free cannabis products to help treat ailments like PTSD, Chronic Pain and more.

Not only does Operation Grow4Vets provide cannabis to veterans, but they donate grow equipment and help veterans find jobs in the cannabis industry as well.

<http://www.medicaljane.com/directory/company/operation-grow4vets/>

<http://www.medicaljane.com/2013/01/05/veterans-and-medical-marijuana/>

<http://www.medicaljane.com/2014/07/11/israeli-study-orally-administered-tetrahydrocannabinol-thc-may-help-treat-ptsd/>

Preliminary, open-label, pilot study of add-on oral Δ 9-tetrahydrocannabinol in chronic post-traumatic stress disorder.

Abstract

BACKGROUND AND OBJECTIVES:

Many patients with post-traumatic stress disorder (PTSD) achieve but partial remission with current treatments. Patients with unremitted PTSD show high rates of substance abuse. Marijuana is often used as compassion add-on therapy for treatment-resistant PTSD. This open-label study evaluates the tolerance and safety of orally absorbable Δ (9)-tetrahydrocannabinol (THC) for chronic PTSD.

METHODS:

Ten outpatients with chronic PTSD, on stable medication, received 5 mg of Δ (9)-THC twice a day as add-on treatment.

RESULTS:

There were mild adverse effects in three patients, none of which led to treatment discontinuation. The intervention caused a statistically significant improvement in global symptom severity, sleep quality, frequency of nightmares, and PTSD hyper arousal symptoms.

CONCLUSIONS:

Orally absorbable Δ (9)-THC was safe and well tolerated by patients with chronic PTSD.

<http://www.ncbi.nlm.nih.gov/pubmed/24935052>

Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study

Three biomarkers examined collectively—OMAR V_T , anandamide and cortisol—correctly classified nearly 85% of PTSD cases. These results suggest that abnormal CB₁ receptor-mediated anandamide signaling is implicated in the etiology of PTSD, and provide a promising neurobiological model to develop novel, evidence-based pharmacotherapies for this disorder.

<http://www.nature.com/mp/journal/v18/n9/full/mp201361a.html>

According to the Department of Veterans Affairs, 7-8% of Americans will be affected with PTSD, which can be quite debilitating.

Michigan joined Connecticut, California, Delaware, Maine, Massachusetts, New Mexico, and Oregon to include PTSD as one of the qualifying conditions to receive medicinal marijuana.

<http://www.medicaljane.com/2014/03/27/ptsd-added-as-qualifying-condition-for-medical-marijuana-in-nevada-shortly-after-michigan/>

US Department of Health and Human Services (HHS) signed off on a University of Arizona study that will investigate the relationship between cannabis and post-traumatic stress disorder (PTSD).

<http://www.medicaljane.com/2014/03/21/us-health-department-approves-clinical-trials-for-cannabis-post-traumatic-stress-ptsd/>

But then it was killed by an Arizona senator

<http://www.mintpressnews.com/ariz-senator-blocks-fed-approved-ptsd-medical-marijuana-research/187973/>

And then the researcher was fired

<http://www.thedailybeast.com/articles/2014/07/10/why-did-america-s-only-pot-researcher-suddenly-get-fired.html>

This was the only current chance for veterans to have a federally approved study. Others, on behalf of veterans, continue to try to receive permission to conduct federally approved research.

Hospice and Palliative Care

Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity

Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.

<http://ajh.sagepub.com/content/28/5/297.abstract>

Sleep Disorders



When we look at the construction of cannabis, we find that it has over 80 cannabinoids. Until recently, tetrahydrocannabinol (THC) was the only cannabinoid anyone seemed to care about. Thankfully recent research, particularly about cannabidiol (CBD), has brought about an intense interest in all the cannabinoids.

As is the case in many of the known cannabinoids, cannabinol (CBN) stems from cannabigerolic acid (CBGA) in cannabis. The plant naturally produces enzymes (aka synthases) that convert the CBGA to one of 3 major cannabinoids: cannabichromene carboxylic acid (CBCA), cannabidiol carboxylic acid (CBDA), and tetrahydrocannabinol carboxylic acid (THCA).

When the plant develops THCA, it usually will be converted to THC as a result of heat or UV light. That being said, THCA can be converted to CBNA over time as well. Prolonged exposure to air causes the THCA to lose hydrogen molecules and oxidize; now we have CBNA. Just like the rest of the acidic cannabinoids, CBNA will convert to cannabinol (CBN) when exposed to heat or UV light.

What Are The Benefits Of Cannabinol (CBN)?

Cannabis is widely used as a sleep-aid for those who suffer from insomnia and cannabinol is the reason why. By all accounts, CBN is the cannabinoid responsible for the sedative effects of cannabis.

<http://www.medicaljane.com/ailment/sleep-disorders/>

<http://www.medicaljane.com/2013/10/31/cannabinoids-could-help-treat-obstructive-sleep-apnea/>

Respiratory Physiology & Neurobiology

Intranodose ganglion injections of dronabinol attenuate serotonin-induced apnea in Sprague-Dawley rat

Obstructive sleep apnea represents a significant public health concern. Afferent vagal activation is implicated in increased apnea susceptibility by reducing upper airway muscle tone via activation of serotonin receptors in the nodose ganglia. Previous investigations demonstrated that systemically administered cannabinoids can be used therapeutically to decrease the apnea/hypopnea index in rats and in humans. However, cannabinoids have effects on both the central and peripheral nervous systems, and the exact mechanism of decreased apnea/hypopnea index with cannabinoids is unknown. Here, we hypothesized that intranodose ganglion injections of a cannabinoid will attenuate 5-HT-induced reflex apnea and increase upper airway muscle tone. We show that dronabinol injected locally into the nodose ganglia suppresses 5-HT-induced reflex apnea, and increases phasic, but not tonic, activation of the genioglossus. These data support the view that dronabinol stabilizes respiratory pattern and augments upper airway muscles by acting at the nodose ganglia. These findings underscore a therapeutic potential of dronabinol for the treatment of obstructive sleep apnea.

<http://www.sciencedirect.com/science/article/pii/S1569904813003273>

<http://www.medicaljane.com/2013/08/19/cannabinol-cbn-will-put-you-to-bed/>

Antibacterial /MRSA Treatment

Antibacterial cannabinoids from Cannabis sativa: a structure-activity study.

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.

<http://www.ncbi.nlm.nih.gov/pubmed/18681481>

Anti-Inflammatory

Prospects for cannabinoids as anti-inflammatory agents.

Abstract

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".

<http://www.ncbi.nlm.nih.gov/pubmed/12532323>

Bowel and Gut

Cannabinoids and the gut: new developments and emerging concepts.

Abstract

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.

<http://www.ncbi.nlm.nih.gov/pubmed/20117132>

Endocannabinoids and the gastrointestinal tract.

Abstract

In the past centuries, different preparations of marijuana have been used for the treatment of gastrointestinal (GI) disorders, such as GI pain, gastroenteritis and diarrhea. Delta9-tetrahydrocannabinol (THC; the active component of marijuana), as well as endogenous and synthetic cannabinoids, exert their biological functions on the gastrointestinal tract by activating two types of cannabinoid receptors, cannabinoid type 1 receptor (CB1 receptor) and cannabinoid type 2 receptor (CB2 receptor). While CB1 receptors are located in the enteric nervous system and in sensory terminals of vagal and spinal neurons and regulate neurotransmitter release, CB2 receptors are mostly distributed in the immune system, with a role presently still difficult to establish. Under pathophysiological conditions, the endocannabinoid system conveys protection to the GI tract, eg from inflammation and abnormally high gastric and enteric secretion. For such protective activities, the endocannabinoid system may represent a new promising therapeutic target against different GI disorders, including frankly inflammatory bowel diseases (eg, Crohn's disease), functional bowel diseases (eg, irritable bowel syndrome), and secretion- and motility-related disorders.

<http://www.ncbi.nlm.nih.gov/pubmed/16751708>

Gut feelings about the endocannabinoid system.

Abstract

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.

<http://www.ncbi.nlm.nih.gov/pubmed/21481098>

Gastrointestinal endocannabinoid system: multifaceted roles in the healthy and inflamed intestine.

Abstract

1. The endogenous cannabinoid (endocannabinoid) system is emerging as a key modulator of intestinal physiology, influencing motility, secretion, epithelial integrity and immune function in the gut, in addition to influencing satiety and emesis. 2. Accumulating evidence suggests that the endocannabinoid system may play a pivotal role in the pathophysiology of gastrointestinal disease, particularly in the light of recent studies demonstrating an effect of endocannabinoids on the development of experimental inflammation and linkages with functional clinical disorders characterized by altered motility. 3. The predominant endocannabinoids, anandamide and 2-arachidonoylglycerol, not only mediate their effects via two recognized cannabinoid receptor subtypes, namely CB(1) and CB(2), but emerging evidence now shows they are also substrates for cyclo-oxygenase (COX)-2, generating a distinct and novel class of prostaglandin ethanolamides (prostamides) and prostaglandin glycerol esters. These compounds are bioactive and may mediate an array of biological effects distinct to those of conventional prostanoids. 4. The effects of prostamides on gastrointestinal motility, secretion, sensation and immune function have not been characterized extensively. Prostamides may play an important role in gastrointestinal inflammation, particularly given the enhanced expression of both COX-2 and endocannabinoids that occurs in the inflamed gut. 5. Further preclinical studies are needed to determine the therapeutic potential of drugs targeting the endocannabinoid system in functional and inflammatory gut disorders, to assist with the determination of feasibility for clinical translation.

<http://www.ncbi.nlm.nih.gov/pubmed/18671715>

Cannabinoids for gastrointestinal diseases: potential therapeutic applications.

Abstract

Delta(9)-Tetrahydrocannabinol (the active ingredient of marijuana), as well as endogenous and synthetic cannabinoids, exert many biological functions by activating two types of cannabinoid receptors, CB(1) and CB(2) receptors. CB(1) receptors have been detected on enteric nerves, and pharmacological effects of their activation include gastroprotection, reduction of gastric and intestinal motility and reduction of intestinal secretion. The digestive tract also contains endogenous cannabinoids (i.e., the endocannabinoids anandamide and 2-arachidonylglycerol) and mechanisms for endocannabinoid inactivation (i.e., endocannabinoids uptake and enzymatic degradation). Cannabinoid receptors, endocannabinoids and the proteins involved in endocannabinoids inactivation are collectively referred as the 'endogenous cannabinoid system'. A pharmacological modulation of the endogenous cannabinoid system could provide new therapeutics for the treatment of a number of gastrointestinal diseases, including nausea and vomiting, gastric ulcers, irritable bowel syndrome, Crohn's disease, secretory diarrhea, paralytic ileus and gastro esophageal reflux disease. Some cannabinoids are already in use clinically, for example, nabilone and delta(9)-tetrahydrocannabinol are used as antiemetics.

<http://www.ncbi.nlm.nih.gov/pubmed/12517253>

The endocannabinoid system and gut-brain signaling.

Abstract

The endocannabinoid system (ECS) consists of cannabinoid receptors, endogenous ligands and the biosynthetic and metabolic enzymes for their formation and degradation. Within the gastrointestinal (GI) tract, the ECS is involved in the regulation of motility, secretion, sensation, emesis, satiety and inflammation. Recent studies examining the ECS in the gut-brain axis have shed new light on this system and reveal many facets of regulation that are amenable to targeting by pharmacological interventions that may prove valuable for the treatment of GI disorders. In particular, it has been shown that endocannabinoid levels in the brain and gut vary according to states of satiety, and in conditions of diarrhea, emesis and inflammation. The expression of cannabinoid (CB)(1) receptors on vagal afferents is controlled by the states of satiety and by gut peptides such as cholecystokinin and ghrelin. Vagal control of gut motor function and emesis is regulated by endocannabinoids in the brainstem acting on CB(1), CB(2) and transient receptor potential vanilloid (TRPV)-1 receptors. The ECS is involved in the modulation of visceral sensation and likely contributes to effects of stress on GI function. This review examines recent developments in our understanding of the ECS in gut-brain signaling.

<http://www.ncbi.nlm.nih.gov/pubmed/17904903>

Nausea, Vomiting, Appetite

Despite the effect cannabis has on nausea, there is not much information available as to why. A recent study, published in the British Journal of Pharmacology, investigated nausea's relationship with two cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD). The researchers first treated rats with THC, CBD, or rimonabant to test whether the substance would induce nausea. As expected, the rimonabant produced a nauseous reaction, whereas the cannabinoids did not. Combining that with the fact THC is believed to be an appetite suppressant, it may represent a safe alternative for rimonabant in fighting obesity. The next step of the study was to test the effect of cannabinoids on nausea. Researchers induced nausea in the rats with a toxin and treated them with 10-20 mg of THC or CBD. According to their results, both cannabinoids reduced the rats' experience with nausea.

According to the study's author, tetrahydrocannabivarin (THCV) and cannabidvarin (CBDV) "may have therapeutic potential in reducing nausea." While the idea of using cannabis to treat nausea is nothing new, this study is another step towards understanding the role of each cannabinoid.

<http://www.medicaljane.com/ailment/nausea-vomiting/>

<http://www.medicaljane.com/2013/07/24/the-endocannabinoid-system-cannabis-appetite/>

<http://www.medicaljane.com/2013/09/03/cannabinoids-show-potential-in-reducing-nausea/>

Bladder Health

As we know, multiple sclerosis (MS) patients have reported success using cannabis to battle the symptoms. Usually, medical marijuana is credited with reducing the number of spasms, but recent reports suggest that it could improve bladder functioning as well.

A 2004 uro-neurology case study from London suggested, "cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS." The study opened the door to a world of questions, and new research may offer some answers.

Activation Of The CB1 Receptor May Improve Bladder Function

BJU International recently published a German study that investigated the relationship between the CB1 receptor and bladder function. The team of researchers, led by Claudius Fullhase, compared the bladder function of 20 wild mice to that of 20 mice born without CB1 receptors.

<http://www.medicaljane.com/2013/10/02/german-study-cannabinoids-may-serve-a-role-in-bladder-function/>

An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis.

Abstract

The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated the safety, tolerability, dose range, and efficacy of two whole-plant extracts of Cannabis sativa in patients with advanced MS and refractory LUTS. Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment ($P < 0.05$, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly ($P < 0.05$, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based

medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS.

<http://www.ncbi.nlm.nih.gov/pubmed/15327041>

Bladder function in a cannabinoid receptor type 1 knockout mouse

Conclusions

In vitro, bladder strips from CB1 KO mice responded to muscarinic receptor stimulation similarly as the WT controls, but were less responsive to electrical stimulation of nerves. In vivo, CB1 KO mice had a higher micturition frequency and more spontaneous activity than WT mice.

The present findings suggest that CB1 receptors are involved in peripheral and central nervous control of micturition.

<http://onlinelibrary.wiley.com/doi/10.1111/bju.12350/abstract>

Cannabinoids Used in Treating Drug Addiction

Study: Cannabidiol (CBD) May Reduce Cigarette Consumption

<http://www.medicaljane.com/2013/10/25/study-cannabidiol-cbd-may-reduce-cigarette-consumption/>

Addictive Behaviors

Volume 38, Issue 9, September 2013, Pages 2433–2436

Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings

Abstract

The role of the endocannabinoid system in nicotine addiction is being increasingly acknowledged. We conducted a pilot, randomised double blind placebo controlled study set out to assess the impact of the ad-hoc use of cannabidiol (CBD) in smokers who wished to stop smoking. 24 smokers were randomized to receive an inhaler of CBD (n = 12) or placebo (n = 12) for one week, they were instructed to use the inhaler when they felt the urge to smoke. Over the treatment week, placebo treated smokers showed no differences in number of cigarettes smoked. In contrast, those treated with CBD significantly reduced the number of cigarettes smoked by ~ 40% during treatment. Results also indicated some maintenance of this effect at follow-up. These preliminary data, combined with the strong preclinical rationale for use of this compound, suggest CBD to be a potential treatment for nicotine addiction that warrants further exploration.

<http://www.sciencedirect.com/science/article/pii/S030646031300083X>

<http://www.medicaljane.com/2013/09/13/cannabis-topicals-study-cannabis-topicals-may-aid-in-alcoholism-treatment-aid-in-alcoholism-treatment/>

<http://www.medicaljane.com/2014/01/15/study-cannabidiol-cbd-may-help-prevent-alcohol-induced-liver-damage/>

"The present findings may point to novel interventions to be employed during treatment for opiate dependence that specifically target cannabinoid-opioid system interactions" - Thomas Jefferson University, Philadelphia.

CONCLUSIONS AND SCIENTIFIC SIGNIFICANCE:

The present findings may point to novel interventions to be employed during treatment for opiate dependence that specifically target cannabinoid-opioid system interactions.

According to the Thomas Jefferson University study, cannabis use before and during treatment decreased the patients score on the Clinical Opiate Withdrawal Scale (COWS). This is a scale used to objectively determine withdrawal symptoms in opiate-dependent patients. The lower scores indicate that cannabis plays a role in reducing the symptoms of opiate withdrawal.

This study suggests that cannabis may play a role in increasing the success of Methadone treatment. The reason for this is that it lowers the amount of withdrawal symptoms patients experience.

As discussed earlier, common symptoms of opiate withdrawal include anxiety, muscle aches, insomnia, abdominal cramps, and nausea. Medical cannabis is already being used to successfully treat each of these symptoms with little to no known side effects. "Marijuana does not have the physical addictive components that opiates do," says Shelley Stormo, a clinical psychologist at Gosnold. "It does not have the propensity, as opiates do, for overdoses. There's no documented death by overdose of marijuana."

<http://www.medicaljane.com/2013/07/21/cannabis-shown-to-ease-opiate-withdrawal/>

Impact of cannabis use during stabilization on methadone maintenance treatment.

CONCLUSIONS AND SCIENTIFIC SIGNIFICANCE:

The present findings may point to novel interventions to be employed during treatment for opiate dependence that specifically target cannabinoid-opioid system interactions.

<http://www.ncbi.nlm.nih.gov/pubmed/23795873>

Opioid Abuse Takes Heavy Toll, Cannabis May Help

While opioids are useful and effective pain management medications, their use and abuse can lead to negative side effects, accidental and intentional death by overdose, and high costs.

Negative side effects caused by opioid use may include, but are not limited to, nausea/vomiting, constipation, dry mouth, sweating, and excessive sleepiness, and in rare cases, difficulty urinating, seizures, hallucinations, bad dreams, confusion, and itchiness. In the United States in 2012,

approximately 16,007 deaths could be attributed to opioid overdose (72% of all pharmaceutical overdose deaths). In 2007, the financial impact of opioid drug abuse totaled over \$55 billion.

Although abuse of and addiction to opioids post-prescription in the chronic pain patient population is rare (approximately 3.27% overall, approximately 0.19% for patients with no previous/current abuse/addiction issues before prescription), withdrawal symptoms may be severe and dependence/tolerance may lead to overdose deaths (as opposed to cannabis dependence, where withdrawal symptoms are mild and overdose death is virtually impossible).

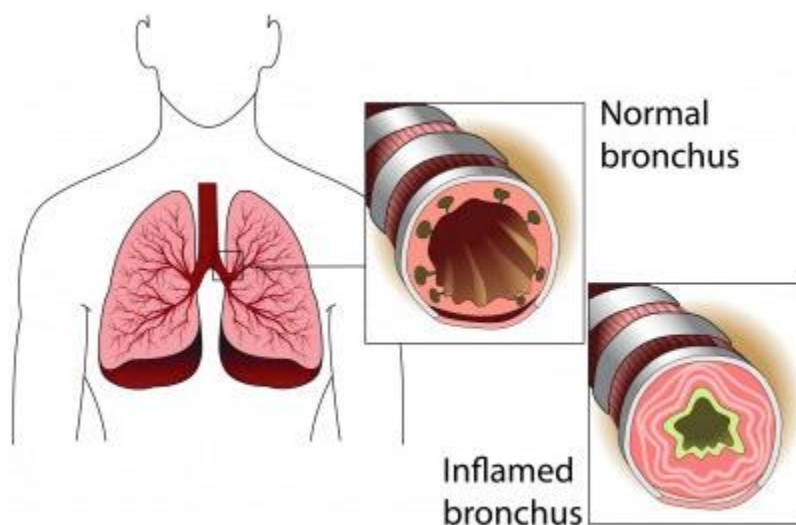
Additionally, a study published in JAMA Internal Medicine in October 2014 found that in states where medical cannabis is legal in the U.S., deaths due to opioid overdose are reduced by approximately 25%.

<http://www.medicaljane.com/2014/12/31/study-study-whole-plant-cannabis-as-add-on-therapy-for-chronic-non-cancer-pain/>

Asthma, COPD

Asthma is one of the most ubiquitous chronic inflammatory diseases in the U.S., affecting an estimated 35 million people, and claiming the lives of 4,000 each year. The disease is typically caused by inflammation of the bronchial tubes, causing the chest to become tight and breathing fairly difficult.

Symptoms include wheezing, coughing (especially at night), shortness of breath, and pain or pressure in the chest. While not every case of asthma is identical, the treatments for all cases are similar.



However, studies have proven that THC acts as a temporary (1-2 hours) bronchodilator, especially when ingested; this is common knowledge by now. The New England Journal of Medicine, published a 1973 study that stated, "Marihuana smoke, unlike cigarette smoke, causes broncho-dilation rather

than broncho-constriction [narrowing of the air passages] and, unlike opiates, does not cause central respiratory depression.”

Additionally, patients suffering from asthma probably do not want to actually smoke marijuana either. Think of heat as a bad thing, especially combustion or fumes from fire. This is exactly why most patients switch to vaporizing their cannabis. Through the use of vaporizers, most people claim they can stay medicated, without the harmful side effects of smoke (of any sort).

<http://www.medicaljane.com/2013/02/02/asthma-and-cannabis-marijuana-shown-to-manage-asthma-symptoms/>

Cannabinoid effects on ventilation and breathlessness: a pilot study of efficacy and safety.

Abstract

Based on the neurophysiology of dyspnoea and the distribution of cannabinoid receptors within the central nervous system, we hypothesize that the unpleasantness of breathlessness will be ameliorated in humans by cannabinoids, without respiratory depression. ...After drug administration, COPD subjects picked 'air hunger' breathlessness descriptors less frequently compared to placebo. We have shown that breathlessness descriptors may detect an amelioration of the unpleasantness of breathlessness by cannabinoids without a change in conventional breathlessness ratings (VAS). A stimulus more specific for air hunger may be needed to demonstrate directly a drug effect on breathlessness. However, this study shows that the inclusion of respiratory descriptors may contribute to the assessment of drug effects on breathlessness.

<http://www.ncbi.nlm.nih.gov/pubmed/21436223>

Bone Disease

Role of cannabinoid receptors in bone disorders: alternatives for treatment.

Abstract

A number of recent preclinical studies have demonstrated the potential role of cannabinoids and their receptors in bone metabolism. Pharmacological and genetic modulation of cannabinoid receptors indicate that cannabinoid ligands may provide attractive and novel agents for the treatment of bone diseases. This article reviews the role of cannabinoid receptors in regulating bone mass, bone loss and bone cell function in health and disease. The article also provides support to the notion that cannabinoid receptor ligands show a great promise in the treatment of bone diseases associated with accelerated osteoclastic bone resorption including osteoporosis, rheumatoid arthritis and bone metastasis.

<http://www.ncbi.nlm.nih.gov/pubmed/19221634>

Epilepsy and Seizures

The case for medical marijuana in epilepsy.

Abstract

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. Much more needs to be learned about the mechanisms of antiepileptic activity of the phytocannabinoids and other constituents of Cannabis sativa.

<http://www.ncbi.nlm.nih.gov/pubmed/24854149>

Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy.

Abstract

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 <http://www.ncbi.nlm.nih.gov/pubmed/24237632>

Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism.

Abstract

BACKGROUND AND PURPOSE:

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.

EXPERIMENTAL APPROACH:

The anticonvulsant profiles of two CBDV BDSs (50-422 mg·kg⁻¹) were evaluated in three animal models of acute seizure. Purified CBDV and CBD were also evaluated in an isobolographic study to evaluate potential pharmacological interactions. CBDV BDS effects on motor function were also investigated using static beam and grip strength assays. Binding of CBDV BDSs to cannabinoid CB1 receptors was evaluated using displacement binding assays.

KEY RESULTS:

CBDV BDSs exerted significant anticonvulsant effects in the pentylenetetrazole (≥ 100 mg·kg⁻¹) and audiogenic seizure models (≥ 87 mg·kg⁻¹), and suppressed pilocarpine-induced convulsions (≥ 100 mg·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.

CONCLUSIONS AND IMPLICATIONS:

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.

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<http://www.ncbi.nlm.nih.gov/pubmed/23902406>