Medicinal Cannabis
Potential Benefits – Potential and Known Risks
CBD and THC

Edward Redd MD
Sept 2015
ON THE HASCHISCH OR CANNABIS INDICA.

BY JOHN BELL, M.D., DERRY, N. H.

[Communicated for the Boston Medical and Surgical Journal.]

The various periodicals of this country have abounded, during the last few years, with accounts of the Haschisch; every experimenter giving the history of the effects it has had upon himself. In most cases this has been mingled with much fanciful and irrelevant matter. These notices have been confined almost exclusively to the various popular literary journals, but it has not received the attention it merits in those exclusively devoted to medicine. Under these circumstances, the following résumé of what has been written on the subject, seen through the medium of personal experience, may not be destitute of interest.
Page 197 “When given in full doses, cannabis indica produces a feeling of exhilaration, with a condition of revery, and a train of mental and nervous phenomena which varies very much according to the temperament or idiosyncrasies of the subject……
Page 197 continued. “The sensations are generally spoken of as very pleasurable; often beautiful visions float before the eyes, and sense of ecstasy fill the whole being; sometimes the venereal appetites are greatly excited; sometimes loud laughter, constant giggling, and other indications of mirth are present.”
Page 201. “Sooner or later if the dose be sufficient, drowsiness comes on...often with partial loss of strength...especially in the lower limbs. The Pupils are dilated, the pulse is quickened, and finally the subject falls into a heavy sleep, out of which he generally awakes hungry, without any of the wretched gastric sensations or the malaise felt after an opiate. Confusion of thought however may persist for hours”
Page 200 “In some cases Indian hemp produces....marked disturbances of motility. Convulsions have been noticed by Dr. Lawrie and local spasms with salaam convulsions by Dr. F. H. Brown. According to Dr. O’Shaughnessy, the induction of epilepsy is not rare among the Hindoos.”
That the drug has very little influence upon the vital functions is shown by the enormous amounts required in Dr. Hare’s experiments to kill.

Hemp is not a dangerous drug; even the largest doses of its active preparation, although causing most alarming symptoms, do not compromise life. No case of acute poisoning by it terminating fatally has, that I am aware of, been reported.
As an analgesic, it is very much inferior to opium, but may be tried when the latter is for any reason contra-indicated. In full doses, in neuralgic pains, it certainly often gives relief.

“It has been very largely employed to induce euthanasia in the advanced stages of phtisis, and constitutes, it is said, a popular nostrum employed for that purpose.” (Note: phtisis is likely end-stage tuberculosis)
Page 201. “In tetanus, Indian hemp has been used quite largely....Dr. Roemer (St. Louis Medical and Surgical Journal p 363, 1873) has collected thirty-five cases, with twenty-one recoveries and fourteen deaths.”

“As suggested by Dr. Sequin of New York, cannabis indica is sometimes of value in the treatment of migraine. It should be given continuous day after day, for months, in such doses as will keep just within the limit of distinct physiological effects.”
“Under the name of tannate of cannabene the German chemist Merck has put upon the market a preparation of cannabis, which is affirmed by Fronmuller (Memorabilien, 1882, 257) and by Hiller (Berlin. Klin. Wochensch., 1883, ix. 125) to be a very valuable hypnotic in doses from four to seven grains.”
Fast Forward 125 years.....
• P 38. Vivek Murthy, the U.S. surgeon general, commenting on marijuana, “for certain medical conditions and symptoms it can be helpful.”

• P 39. “It’s also thought to be useful as, among other things, an analgesic, an antiemetic, a bronchodilator, and an anti-inflammatory..... may protect the brain against trauma, boost the immune system, and aid in “memory extinction” after catastrophic events.”
Legalized in 23 states for medicinal use

• The federal government has chosen to not enforce some federal marijuana laws or prosecute medicinal and recreational use

• Medicinal Marijuana
  – Each state has a list of conditions for which it can be used

• Each state has various restrictions:
  – Regulated growers and centralized dispensaries
    • State-run vs. commercial vs. grow-your-own
  – Grow your own – restrictions on number of plants
  – Limitations on how much can be dispensed per month or possessed
What uses do the advocates claim?
What diagnoses do states allow?

• Pain
• Neuropathy pain
• MS spasticity
• Seizures
• Anxiety
• PTSD
• Schizophrenia
• TBI
• Headaches
• Chronic pancreatitis
• Irritable bowel syndrome
• Intractable nausea
• Treatment of brain cancer and other cancers
• Parkinson’s disease
• Prevention/treatment of Alzheimer’s disease
• Arthritis
• Crohn’s disease/inflammatory bowel disease
• HIV/AIDS cachexia
• Spinal cord injury
• ALS
• MS
• Terminal illness with life expectancy < 1 year
Pot Science

- Endocannabinoid system
- Endocannabinoids
- Phytocannabinoids
  - Tetrahydrocannabinol – THC
  - Cannabidiol – CBD
  - Adverse effects of phytocannabinoids
- Potential for clinical use of phytocannabinoids
  - Risk/Benefit
  - What is known?
  - What is suspected?
  - What is unknown?
- Problems with marijuana as a pharmaceutical
- Bypassing the FDA and IRB
  - Risk/Benefit
Endocannabinoid system

- Endocannabinoids = Chemical transmitters released by cells that attach to receptors on other cells acting as messengers and signalers.
- Circuit breaker in the brain
- Inflammation and repair of neuron injury
- Enteric neuron function in the gut
- Immune function and inflammation response
- Metabolism - energy storage – feeding & lipogenesis
- Cell life cycle regulation – apoptosis and cell death
- When the endocannabinoid system is not working properly, disease happens.
Nature Medicine 2008 14;9, 923-930
Nature Medicine
2008 14;9, 923-930
CB1 receptor activation $\rightarrow$ suppression of Calcium influx $\rightarrow$ stops the neuron from firing
What happens if CB1 receptors are blocked or destroyed or down-regulated?
Anandamide and 2 AG

THC activates CB1 like anandamide
Nerve injury and chronic pain

Immune responses to peripheral nerve injury

- Astrocite
- Neuron
- Microglia

Peripheral nerve injury

- Schwann cells

Microglia activation

- CCR2
- iNOS

Neuropathic pain

- IFN-γ
Endocannabinoid effects in the GI tract

- Anandamide
  - Inflammatory/immune cells: CB₂
  - Myenteric neurons: CB₁
  - Submucosal neurons: CB₁
  - Epithelial cells: CB₂

- Inflammatory mediators
- Intestinal hypermotility
- Intestinal hypersecretion
- Epithelial wounds: visceral pain
- Visceral pain

Beneficial effects in inflammation

Gut.BMJ.com
Average THC and CBD Levels in the US: 1960 - 2011

THC: Psychoactive Ingredient

CBD: NON-Psychoactive Ingredient

Mehmedic et al., 2010

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Figure 1. Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin.

Panel A shows the increasing potency of marijuana (i.e., the percentage of THC) in samples seized by the Drug Enforcement Administration (DEA) between 1995 and 2012. Panel B provides estimates of the number of emergency department visits involving the use of selected illicit drugs (marijuana, cocaine, and heroin) either singly or in combination with other drugs between 2004 and 2011. Among these three drugs, only marijuana, used either in combination with other drugs or alone, was associated with significant increases in the number of visits during this period (a 62% increase when used in combination with other drugs and a 100% increase when used alone, P<0.05 for the two comparisons).
B Reported Daily Use of Cigarettes or Marijuana

Daily cigarette use in previous 30 days

Daily marijuana use in previous 30 days

Grade 12 Students (%)

NEJM (2014) 370;23,2219-2227
“Perceived risk” = % of Grade 12 students who reported that the use of marijuana is “dangerous.”
NEJM 370;23, 2219-2227
Quest Diagnostics Drug Test Index™

Workplace Pos MJ Tests: Increase from 2012-2013

http://www.questdiagnostics.com/home/physicians/health-trends/drug-testing
Vaporizing industries: Nicotine and Marijuana

**Pax by Ploom**

- Japan Tobacco International (JTI) is the third largest international tobacco company behind Philip Morris International.

- In 2011, JTI bought a portion of Ploom, a startup based in Silicon Valley that produces a loose-leaf vaporizer that can be used to inhale heated vapor from *marijuana* as well as *tobacco*, called the Pax.
Cannabis: Adverse Effects – Short-Term Use

- Impaired short-term memory,
  - Difficulty learning and retaining information
- Impaired motor coordination,
  - Impaired driving skills → MVA’s
  - Increased risk of injuries
- Altered judgment
  - Risk of sexual behaviors that lead to STD’s
- Potent or high doses → paranoia and psychosis

Average THC and CBD Levels in the US: 1960 - 2011

THC: Psychoactive Ingredient

CBD: NON-Psychoactive Ingredient

Mehmedic et al., 2010

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Cannabis: Adverse Effects – Long-term Use

• Addiction
  – 9% of users overall,
  – 17% of those who begin use in adolescence,*
  – 25 to 50% of those who are daily users*

• Altered brain development*

• Poor educational outcome, with increased likelihood of dropping out of school*

• Cognitive impairment, with lower IQ among those who were frequent users during adolescence*

• Diminished life satisfaction and achievement *
  – (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*

• Symptoms of chronic bronchitis

• Increased risk of chronic psychotic disorders including schizophrenia (in persons with a genetic predisposition to such disorders)

*Strongly associated with initial use early in adolescence

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.
Reductions in IQ

Dunedin prospective study of 1037 Ss born 1972/73, tested for IQ at age 13 and 38y. Tested THC use ages 18, 21, 26, 32 and 38y.

Adolescent Vulnerability

Change in Full-Scale IQ (in standard deviation units)

1 Diagnosis
- Cannabis Dependent: n=17
- Not Cannabis Dependent: n=57
- p = .44

2 Diagnoses
- Cannabis Dependent: n=12
- Not Cannabis Dependent: n=21
- p = .09

3 Diagnoses
- Cannabis Dependent: n=23
- Not Cannabis Dependent: n=14
- p = .02

Early Marijuana Use and Intensity of Use are Associated with Educational Attainment

High School Completion

- Low Intensity
  - < Age 14: -12%**
  - > Age 14: -1%

- Med/High Intensity
  - < Age 14: -28%***
  - > Age 14: -11%***

Young people who begin marijuana use at a young age and use it intensively have a higher probability of dropping out of high school.

University Entrance Score

- < Age 14
  - Low Intensity: -2.4%
  - Med/High Intensity: 10.1%*

- > Age 14
  - Low Intensity: 0.4%
  - Med/High Intensity: -1.9%

For those that do successfully complete high school and obtain a university entrance score, med-high intensity use is associated with scores on average 10 percentiles lower than their peers.

*** p<0.01, ** p<0.05

Effect of long-term cannabis use on axonal fibre connectivity

Figure 5 Age at which regular cannabis use commenced was correlated with radial and axial diffusivity in the fimbria (A) and commissural pathways extending to the precuneus (B). Biological age was included as a nuisance covariate. Each data point, depicted as a cross, represents the average of the diffusivity measure over all cannabis users of the same age of regular use.
Increased risk (40-100%) of psychotic and affective mental health outcomes

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis

Summary

Background Whether cannabis can cause psychotic or affective symptoms that persist beyond transient intoxication is unclear. We systematically reviewed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes.

Methods We searched Medline, Embase, CINAHL, PsycINFO, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, and MEDCARIB from their inception to September, 2006, searched reference lists of studies selected for inclusion, and contacted experts. Studies were included if longitudinal and population based. 35 studies from 4804 references were included. Data extraction and quality assessment were done independently and in duplicate.

Findings There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1·41, 95% CI 1·20–1·65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2·09, 1·54–2·84). Results of analyses restricted to studies of more clinically relevant psychotic disorders were similar. Depression, suicidal thoughts, and anxiety outcomes were examined separately. Findings for these outcomes were less consistent, and fewer attempts were made to address non-causal explanations, than for psychosis. A substantial confounding effect was present for both psychotic and affective outcomes.

Lancet 2007; 370:319-28
Cannabis and psychosis

David M Fergusson, Richie Poulton, Paul F Smith, Joseph M Boden

The UK government is considering reclassifying cannabis because of concerns about links with mental health problems. What does the evidence show?

Summary of prospective studies of cannabis use and psychotic symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Assessment</th>
<th>Outcome measure</th>
<th>Adjusted association between cannabis and psychosis* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreasson et al¹</td>
<td>45,570 male Swedish military conscripts aged 18-21</td>
<td>At 15 year follow-up</td>
<td>Clinical diagnosis of schizophrenia</td>
<td>Highest level of use: Relative risk 2.3 (1.0 to 5.3)</td>
</tr>
<tr>
<td>Arsenault et al²</td>
<td>759 members of New Zealand birth cohort</td>
<td>At age 26</td>
<td>DSM-IV criteria for schizophreniform disorder</td>
<td>Cannabis users by age 15: Odds ratio 1.95 (0.76 to 5.01)</td>
</tr>
<tr>
<td>Caspi et al³</td>
<td>803 members of New Zealand birth cohort</td>
<td>At age 26</td>
<td>DSM-IV criteria for schizophreniform disorder</td>
<td>Participants with Val/Val variant of COMT gene: Odds ratio 10.9 (2.2 to 54.1)</td>
</tr>
<tr>
<td>Fergusson et al⁴</td>
<td>1055 members of New Zealand birth cohort</td>
<td>At age 25</td>
<td>No of psychotic symptoms in past month†</td>
<td>Daily cannabis users: Incident rate ratio=1.77 (1.28 to 2.44)</td>
</tr>
<tr>
<td>Henquet et al⁵</td>
<td>2437 German participants aged 14 to 24</td>
<td>At baseline and four year follow up</td>
<td>At least one “broad” or two “narrow” psychosis outcomes‡</td>
<td>Daily cannabis users: Odds ratio 2.23 (1.30 to 3.84)</td>
</tr>
<tr>
<td>van Os et al⁶</td>
<td>4104 participants in Dutch general population study</td>
<td>Assessed three times over four years</td>
<td>≥1 positive rating on psychotic symptom items§</td>
<td>Highest level of use: Odds ratio 6.81 (1.79 to 25.92)</td>
</tr>
</tbody>
</table>

*Compared with non-users.
†Scored on 10 items from symptom checklist (SCL-90).
‡Composite international diagnostic interview (Munich version).
§Brief psychiatric rating scale.

Epidemiological evidence suggests a persistent association between cannabis use and psychosis that is robust to methodological challenges.

Neuroscientific studies show that cannabis may lead to psychosis through effects on the processing of dopamine in the brain.

Taken together, this evidence suggests a causal relation in which frequent use of cannabis leads to a greater risk of psychotic symptoms.
The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene. Caspi et al, BIOL PSYCHIATRY 2005;57:1117–1127

Table 3. Comparisons of the Three (Genotype) by Two (Adolescent-Onset Cannabis Use) Groups on Covariates and Outcomes

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Non-Cannabis-Using Adolescents</th>
<th>Early-Onset Adolescent Cannabis Users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Met/Met (n = 151)</td>
<td>Val/Met (n = 311)</td>
</tr>
<tr>
<td>Adult cannabis use (%)</td>
<td>21.8</td>
<td>25.2</td>
</tr>
<tr>
<td>Adolescent use of drugs other than</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>cannabis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult use of amphetamines and</td>
<td>15.2</td>
<td>16.7</td>
</tr>
<tr>
<td>hallucinogens (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood psychotic symptoms (%)</td>
<td>15.4</td>
<td>10.0</td>
</tr>
<tr>
<td>Childhood IQ (M, SD)</td>
<td>110 (13)</td>
<td>107 (13)</td>
</tr>
<tr>
<td>Adolescent conduct disorder (%)</td>
<td>10.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Diagnosis of schizophreniform</td>
<td>4.0</td>
<td>2.3</td>
</tr>
<tr>
<td>disorder (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reports of psychotic symptoms</td>
<td>.96 (2.8)</td>
<td>.99 (2.8)</td>
</tr>
<tr>
<td>(M, SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of hallucinatory experiences</td>
<td>12.6</td>
<td>9.7</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of delusional beliefs (%)</td>
<td>14.6</td>
<td>16.4</td>
</tr>
<tr>
<td>Informant reports of psychotic symptoms</td>
<td>.42 (.71)</td>
<td>.33 (.54)</td>
</tr>
</tbody>
</table>

Notes:

*The covariates offer alternative explanations of the obtained G × E results. There was no significant association between genotype and any of the covariates (all p values exceed .35). There was a significant association between adolescent-onset cannabis use and adult cannabis use (p < .001), use of other drugs in adolescence (p < .001), use of amphetamines and hallucinogens in adulthood (p < .001), and adolescent conduct disorder (p < .001), but not between adolescent-onset cannabis use and childhood psychotic symptoms (p = .06) and childhood IQ (p = .27). Moreover, the observed G × E interaction could not be accounted for by the pattern of associations in the six exposure cells; that is, when stratified by adolescent-onset cannabis use, the three genotype groups did not differ from each other on any of the covariates.

*Percent study members reporting using cannabis, on average, on a monthly basis at age 21 years, 26 years, or both.

*Percent study members reporting trying other drugs at age 15 years, 18 years, or both.

*Percent study members reporting using amphetamines, hallucinogens, or both at age 21 years, 26 years, or both.

*Percent study members reporting “strong” or “weak” psychotic symptoms at age 11 years.

*Percent study members meeting diagnostic criteria for conduct disorder between ages 11 and 18 years.
The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene. Caspi et al, BIOL PSYCHIATRY 2005;57:1117–1127
Medicinal benefits......

• Marijuana vs. Hemp
• THC
• CBD
• Numerous other phytocannabinoids
• Cannabis based medicine (CBM)
• Synthetic cannabinoids
  – Marinol
  – Others
IMPORTANCE As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration-approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.
Clinical Conditions with Symptoms That May Be Relieved by Treatment with Marijuana or Other Cannabinoids.

Glaucoma
Early evidence of the benefits of marijuana in patients with glaucoma (a disease associated with increased pressure in the eye) may be consistent with its ability to effect a transient decrease in intraocular pressure, but other, standard treatments are currently more effective. THC, cannabidiol, and nabilone (a synthetic cannabinoid similar to THC), but not cannabidiol, were shown to lower intraocular pressure in rabbits. More research is needed to establish whether molecules that modulate the endocannabinoid system may not only reduce intraocular pressure but also provide a neuroprotective benefit in patients with glaucoma.

Nausea
Treatment of the nausea and vomiting associated with chemotherapy was one of the first medical uses of THC and other cannabinoids. THC is an effective antiemetic agent in patients undergoing chemotherapy, but patients often state that marijuana is more effective in suppressing nausea. Other, unidentified compounds in marijuana may enhance the effect of THC (as appears to be the case with THC and cannabidiol, which operate through different antiemetic mechanisms). Paradoxically, increased vomiting (hyperemesis) has been reported with repeated marijuana use.

AIDS-associated anorexia and wasting syndrome
Reports have indicated that smoked or ingested cannabis improves appetite and leads to weight gain and improved mood and quality of life among patients with AIDS. However, there is no long-term or rigorous evidence of a sustained effect of cannabis on AIDS-related morbidity and mortality, with an acceptable safety profile, that would justify its incorporation into current clinical practice for patients who are receiving effective antiretroviral therapy. Data from the few studies that have explored the potential therapeutic value of cannabinoids for this patient population are inconclusive.

Chronic pain
Marijuana has been used to relieve pain for centuries. Studies have shown that cannabinoids acting through central CB1 receptors, and possibly peripheral CB1 and CB2 receptors, play important roles in modeling nociceptive responses in various models of pain. These findings are consistent with reports that marijuana may be effective in ameliorating neuropathic pain, even at very low levels of THC (1.29%). Both marijuana and dronabinol, a pharmaceutical formulation of THC, decrease pain, but dronabinol may lead to longer-lasting reductions in pain sensitivity and lower ratings of rewarding effects.

Inflammation
Cannabinoids (e.g., THC and cannabidiol) have substantial antiinflammatory effects because of their ability to induce apoptosis, inhibit cell proliferation, and suppress cytokine production. Cannabidiol has attracted particular interest as an antiinflammatory agent because of its lack of psychoactive effects. Animal models have shown that cannabidiol is a promising candidate for the treatment of rheumatoid arthritis and for inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis and Crohn’s disease).

Multiple sclerosis
Nabiximols (Sativex, GW Pharmaceuticals), an oromucosal spray that delivers a mix of THC and cannabidiol, appears to be an effective treatment for neuropathic pain, disturbed sleep, and spasticity in patients with multiple sclerosis. Sativex is available in the United Kingdom, Canada, and several other countries and is currently being reviewed in phase 3 trials in the United States in order to gain approval from the Food and Drug Administration.

Epilepsy
In a recent small survey of parents who use marijuana with a high cannabidiol content to treat epileptic seizures in their children, 11% (2 families out of the 19 that met the inclusion criteria) reported complete freedom from seizures, 42% (8 families) reported a reduction of more than 80% in seizure frequency, and 32% (6 families) reported a reduction of 25 to 60% in seizure frequency. Although such reports are promising, insufficient safety and efficacy data are available on the use of cannabis botanicals for the treatment of epilepsy. However, there is increasing evidence of the role of cannabidiol as an antiepileptic agent in animal models.

* AIDS denotes acquired immunodeficiency syndrome, CB1 cannabinoid-1 receptor, and CB2 cannabinoid-2 receptor, HIV human immunodeficiency virus, and THC tetrahydrocannabinol.
Chronic Pain

Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions.

- Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone
- Admitted for a 5-day inpatient stay.
- Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2–4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5.
- The extent of chronic pain was also assessed daily.
- Pharmacokinetic investigations showed that using cannabis did not effect blood levels of either morphine or oxycodone.
- Pain was significantly decreased (average 27%, 95% confidence interval 9-46%) after the addition of vaporized cannabis.
- Conclusions: vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels.
- The combination use of cannabis with opioids for treatment of pain may allow for opioid treatment at lower doses with fewer side effects.

*Clinical Pharmacology & Therapeutics* (2011); 90 6, 844–851.
doi: [10.1038/clpt.2011.188](http://doi.org/10.1038/clpt.2011.188)
This systematic review of 18 recent good-quality randomized controlled trials demonstrates that various cannabinoids (natural and synthetic) and combinations of cannabinoids can be modestly effective and relatively safe treatment options for chronic non-cancer (predominantly neuropathic) pain. These studies were all of short duration.

“Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large scale trials of longer duration reporting pain and level of function are required.”
Cancer Pain

Abstract

Objectives. This study compared the efficacy of a tetrahydrocannabinol: cannabinol (THC:CBD) extract, a nonopioid analgesic endocannabinoid system modulator, and a THC extract, with placebo, in relieving pain in patients with advanced cancer.

Methods. In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59).

Results. The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC:CBD compared with placebo (improvement of −1.37 vs. −0.69), whereas the THC group showed a nonsignificant change (−1.01 vs. −0.69). Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical
Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial

Russell K. Portenoy,* Elena Doina Ganae-Motan, Silvia Allende, Ronald Yanagihara, Lauren Shaiova, Sharon Weinstein, Robert McQuade, Stephen Wright, Marie T. Fallon

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Emergency Department, Hospital “Sf. Ioan cel Nou”, Oncology Unit 21, Suceava, Romania.
Department of Palliative Care, National Cancer Institute of Mexico, San Fernando, Mexico.
Medical Oncology, Hazel Hawkins Hospital, Hollister, California.
(Metropolitan Hospital Center, New York, New York.
Huntsman Cancer Institute, Salt Lake City, Utah.
gW Pharmaceuticals plc, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom.
zEdinburgh Cancer Research Center, University of Edinburgh, Crewe Road South, Edinburgh, United Kingdom.


263 patients completed 5-week study.

Average baseline pain score on opioids = 5.8 (4-8).

Lower doses of Nabiximol (THC/CBD) were effective as additive treatment to opioids in managing moderate-severe poorly-controlled cancer pain.

High doses of Nabiximols caused significant side effects and were not statistically significantly better than placebo.

“Nabiximols” is the US generic name for Sativex (GW Pharmaceuticals, UK), a pharmaceutical oral spray that has 2.7mg THC and 2.5 mg of CBD per spray (1:1 ratio).
Inflammation

Cannabinoids (e.g., THC and cannabidiol) have substantial antiinflammatory effects because of their ability to induce apoptosis, inhibit cell proliferation, and suppress cytokine production. Cannabidiol has attracted particular interest as an antiinflammatory agent because of its lack of psychoactive effects. Animal models have shown that cannabidiol is a promising candidate for the treatment of rheumatoid arthritis and for inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis and Crohn’s disease).
Concise Report

Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis

D. R. Blake, P. Robson¹, M. Ho², R. W. Jubb³ and C. S. McCabe

Table 2. Efficacy endpoints: difference between change from baseline between CBM and placebo after 5 weeks of treatment

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Baseline (mean/median)a</th>
<th>Endpoint (mean/median)a</th>
<th>Difference (mean/median)a</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning pain on movementa⁹</td>
<td>7.0</td>
<td>6.7</td>
<td>4.8</td>
<td>5.3</td>
<td>-0.95</td>
</tr>
<tr>
<td>Morning pain at rest⁹</td>
<td>5.3</td>
<td>3.8</td>
<td>3.1</td>
<td>4.1</td>
<td>-1.04</td>
</tr>
<tr>
<td>Morning stiffness⁹</td>
<td>3.5</td>
<td>3.8</td>
<td>3.0</td>
<td>3.2</td>
<td>-0.09</td>
</tr>
<tr>
<td>Quality of sleep</td>
<td>5.7</td>
<td>5.8</td>
<td>3.4</td>
<td>4.6</td>
<td>-1.17</td>
</tr>
<tr>
<td>DAS 28</td>
<td>5.9</td>
<td>6.0</td>
<td>5.0</td>
<td>5.9</td>
<td>-0.76</td>
</tr>
<tr>
<td>SF-MPQ, total intensity of paina (a)</td>
<td>15.0</td>
<td>20.0</td>
<td>10.5</td>
<td>13.0</td>
<td>3.00</td>
</tr>
<tr>
<td>SF-MPQ, intensity of pain at presenta (b)</td>
<td>48.0</td>
<td>50.0</td>
<td>33.0</td>
<td>50.0</td>
<td>-3.00</td>
</tr>
<tr>
<td>SF-MPQ, pain at present (c)</td>
<td>3.2</td>
<td>3.2</td>
<td>2.6</td>
<td>3.3</td>
<td>-0.72</td>
</tr>
</tbody>
</table>

aThese scores were not normally distributed and were therefore analysed non-parametrically (Wilcoxon rank-sum test, Hodges–Lehmann median difference and 95% CI). Other outcomes were subjected to analysis of covariance. SF-MPQ was developed to assess three components of pain: the sensation of pain, its emotional effect and the patient’s cognitive assessment of the pain. Component (a) is a score derived from 15 adjectives describing pain, (b) is a single VAS score and (c) is a verbal rating scale extending from ‘none’ to ‘excruciating’ [10].
Controlled study done in diabetic mice.

- CBD-treated diabetic mice had significant attenuation/reduction of diabetes-induced cardiac dysfunction, oxidative stress, cardiac fibrosis, inflammation, and cell death compared with non-CBD treated diabetic mice.

Collectively, these results coupled with the excellent safety and tolerability profile of CBD in humans, strongly suggest that it may have great therapeutic potential in the treatment of diabetic complications, and perhaps other cardiovascular disorders, by attenuating oxidative/nitrative stress, inflammation, cell death and fibrosis. (J Am Coll Cardiol 2010;56:2115–25) © 2010 by the American College of Cardiology Foundation
A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol

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b University of Washington School of Medicine, Seattle, WA, USA
c University of Montana Department of Pharmaceutical Sciences, MT, USA

Received 15 August 2005; accepted 18 August 2005

Summary This study examines the current knowledge of physiological and clinical effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) and presents a rationale for their combination in pharmaceutical preparations. Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms are explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition. CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported.

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<table>
<thead>
<tr>
<th>Effect</th>
<th>THC</th>
<th>CBD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor/Non-Receptor Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB₁ (CNS/PNS receptors)</td>
<td>++</td>
<td>±</td>
<td>Pertwee (104)</td>
</tr>
<tr>
<td>CB₂ (peripheral receptors)</td>
<td>+</td>
<td>±</td>
<td>Showalter (105)</td>
</tr>
<tr>
<td>Vanilloid (TRPV₁) receptors</td>
<td>-</td>
<td>-</td>
<td>Bisogno (21)</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>+</td>
<td>+</td>
<td>Hampson (73)</td>
</tr>
<tr>
<td>COX-1, COX-2 inhibition</td>
<td>-</td>
<td>-</td>
<td>Stott (106)</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>+</td>
<td>+</td>
<td>Calabria (107), Malfait (20)</td>
</tr>
<tr>
<td><strong>CNS Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>+</td>
<td>++</td>
<td>Wallace (42), Carlini (40)</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>++</td>
<td>+</td>
<td>Collin (61)</td>
</tr>
<tr>
<td>Antinociceptive</td>
<td>++</td>
<td>+</td>
<td>Pertwee (13)</td>
</tr>
<tr>
<td>Psychotropic</td>
<td>++</td>
<td>-</td>
<td>Russo (108)</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>±</td>
<td>++</td>
<td>Zuardi (109)</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>-</td>
<td>++</td>
<td>Zuardi (17), Moreira (78)</td>
</tr>
<tr>
<td>Neuroprotective antioxidant</td>
<td>+</td>
<td>++</td>
<td>Hampson (73)</td>
</tr>
<tr>
<td>Antimetic</td>
<td>++</td>
<td>+</td>
<td>Parker (99)</td>
</tr>
<tr>
<td>Sedation</td>
<td>+</td>
<td>-</td>
<td>Nicholson (55)</td>
</tr>
<tr>
<td>Agitation (Alzheimer disease)</td>
<td>+</td>
<td>-</td>
<td>Volier (79)</td>
</tr>
<tr>
<td>Tic reduction (Tourette syndrome)</td>
<td>+</td>
<td>?</td>
<td>Müller-Vahl (111)</td>
</tr>
<tr>
<td>Opiate withdrawal reduction</td>
<td>+</td>
<td>?</td>
<td>Cichewicz (91), De Vry (36)</td>
</tr>
<tr>
<td>Migraine treatment</td>
<td>+</td>
<td>+</td>
<td>Russo (112)</td>
</tr>
<tr>
<td>Bipolar disease</td>
<td>+</td>
<td>?</td>
<td>Grinspoon (113)</td>
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<tr>
<td>Dystonia</td>
<td>+</td>
<td>+</td>
<td>Consroe (85)</td>
</tr>
<tr>
<td>Parkinsonian symptoms</td>
<td>+</td>
<td>?</td>
<td>Venderova (51)</td>
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<tr>
<td>Withdrawal symptoms to other drugs (reduction)</td>
<td>+</td>
<td>+</td>
<td>Labigiani (89), Dreher (90), De Vry (36)</td>
</tr>
<tr>
<td>Motor neurone disease (ALS) (increased survival, function)</td>
<td>+</td>
<td>+</td>
<td>Raman (81), Abood (82)</td>
</tr>
<tr>
<td><strong>Cardiovascular Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>-</td>
<td>+</td>
<td>Weil (114)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>+</td>
<td>-</td>
<td>Karniol (33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>-</td>
<td>Weil (114)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>-</td>
<td>+</td>
<td>Batkai (115)</td>
</tr>
<tr>
<td><strong>Appetite/Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite</td>
<td>+</td>
<td>-</td>
<td>Pertwee (14)</td>
</tr>
<tr>
<td>GI motility (slowed)</td>
<td>++</td>
<td>+</td>
<td>Pertwee (14)</td>
</tr>
<tr>
<td><strong>Anti-Carcinogenesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioma (apoptosis)</td>
<td>+</td>
<td>+</td>
<td>Sanchez (116), Massi (117)</td>
</tr>
<tr>
<td>Glioma cell migration</td>
<td></td>
<td></td>
<td>Vaccani (98)</td>
</tr>
<tr>
<td><strong>Ophthalmological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-ocular pressure (reduced)</td>
<td>++</td>
<td>+</td>
<td>Jarvinen (118)</td>
</tr>
<tr>
<td>Night vision</td>
<td>+</td>
<td>-</td>
<td>Russo (119)</td>
</tr>
</tbody>
</table>

*Figure 3* Effects of tetrahydrocannabinol (THC) and cannabidiol (CBD), adapted and updated from Russo 2003 [52] ([13, 14, 17, 20, 21, 33, 36, 40, 42, 51, 55, 61, 73, 78, 79, 81, 82, 85, 89–91, 98, 99, 104–109, 111–119]).
Role of Cannabinoid Receptor CB$_2$ in HER2 Pro-oncogenic Signaling in Breast Cancer

**Conclusions:** Our findings reveal an unprecedented role of CB$_2$ as a pivotal regulator of HER2 pro-oncogenic signaling in breast cancer, and they suggest that CB$_2$ may be a biomarker with prognostic value in these tumors.

*JNCI J Natl Cancer Inst, 2015, Vol. 107, No. 6*

Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma

In conclusion, our data indicate that cannabidiol, and possibly *Cannabis* extracts enriched in this natural cannabinoid, represent a promising nonpsychoactive antineoplastic strategy. In particular, for a highly malignant human breast carcinoma cell line, we have shown here that cannabidiol and a cannabidiol-rich extract counteract cell growth both in vivo and in vitro as well as tumor metastasis in vivo. Cannabidiol exerts its effects on these cells through a combination of mechanisms that include either direct or indirect activation of CB$_2$ and TRPV1 receptors and induction of oxidative stress, all contributing to induce apoptosis. Additional investigations are required to understand the mechanism of the growth-inhibitory action of cannabidiol in the other cancer cell lines studied here.
Cannabidiol Enhances the Inhibitory Effects of Δ⁹-Tetrahydrocannabinol on Human Glioblastoma Cell Proliferation and Survival

Jahan P. Marcu¹, Rigel T. Christian¹, Darryl Lau¹, Anne J. Zielinski¹, Maxx P. Horowitz¹, Jasmine Lee¹, Arash Pakdel¹, Juanita Allison¹, Chandani Limbad¹, Dan H. Moore¹,², Garret L. Yount¹, Pierre-Yves Desprez¹, and Sean D. McAllister¹

We therefore tested cannabidiol, the second most abundant plant-derived cannabinoid, in combination with Δ⁹-THC. In the U251 and SF126 glioblastoma cell lines, Δ⁹-THC and cannabidiol acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle and induction of reactive oxygen species and apoptosis as well as specific modulations of extracellular signal-regulated kinase and caspase activities. These specific changes were not observed with either compound individually, indicating that the signal transduction pathways affected by the combination treatment were unique. Our results suggest that the addition of cannabidiol to Δ⁹-THC may improve the overall effectiveness of Δ⁹-THC in the treatment of glioblastoma in cancer patients.

Mol Cancer Ther; 9(1): 180–9. ©2010 AACR.

Authors' Affiliations: ¹California Pacific Medical Center Research Institute and ²Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California
Antitumor Effects of Cannabidiol, a Nonpsychoactive Cannabinoid, on Human Glioma Cell Lines

Paola Massi, Angelo Vaccani, Stefania Ceruti, Arianna Colombo, Maria P. Abbracchio, and Daniela Parolaro

• In conclusion, the nonpsychoactive CBD was able to produce a significant antitumor activity both in vitro and in vivo, thus suggesting a possible application of CBD as an antineoplastic agent.
In conclusion, we have here demonstrated here that the nonpsychotropic phytocannabinoid cannabidiol exerts chemopreventive effects in an experimental model of colon cancer, an effect that is associated with down-regulation of phospho-Akt and up-regulation of caspase-3.

Studies on colorectal carcinoma cells suggest that cannabidiol protects DNA damage caused by an oxidative insult and exerts antiproliferative effects through multiple mechanisms, including involvement of CB1 receptors, TRPV1 and PPARγ.

In the light of its safety records and considering that cannabidiol is already currently used in patients with multiple sclerosis [9], our findings suggest that cannabidiol might be worthy of clinical consideration in colon cancer prevention.

Acknowledgements GA is grateful to Nexus award “Marcello Tonini”.
Conflict of interest This work was partly supported by GW Pharmaceuticals (UK).
Cannabis with high cannabidiol content is associated with fewer psychotic experiences

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a Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Department of Psychiatry, The Netherlands
b Julius Center for Health Sciences and Primary care, University Medical Center Utrecht, The Netherlands

Fig. 2. Mean score on positive symptoms and cannabis exposure per cannabidiol content group (n = 1877).
Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

• Hypothesis: CBD inhibits FAAH $\rightarrow$ increased brain anandamide $\rightarrow$ reduction in psychosis

• DB randomized clinical trial
  – 39 patients hospitalized – acute schizophrenia
  – CBD vs amisulpride (potent antipsychotic that blocks dopamine receptors)

• Measurement of BPRS and PANSS
  – BPRS = Brief Psychiatric Rating Scale
  – PANSS = Positive and Negative Syndrome Scale

• Measurement of anandamide in serum

Leweke et al Transl Psychiatry (2012) 2, e94
Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia

Leweke et al. Transl Psychiatry (2012) 2, e94

Figure 2  Changes from baseline in Positive and Negative Symptoms Scale (PANSS) scores determined using mixed effects repeated measures model analysis (adjusted for baseline). (a) PANSS total score. (b) PANSS-positive score. (c) PANSS-negative score. (d) PANSS general score. Data show predicted means and s.e. at each week. Statistical significance is calculated between groups (\(^ P \leq 0.05\), \(^{**} P \leq 0.01\) and \(^{***} P \leq 0.001\)) and vs baseline (that is, 0; \(^*\)CBD, \(^*\)AMI; \(^{**}/**\)P \leq 0.05, \(^{***}/**\)P \leq 0.01, \(^{###} P \leq 0.001\).
Figure 3 Changes from baseline in side effects determined using mixed effects repeated measures model analysis (adjusted for baseline). (a) Extrapyramidal Symptom Scale (EPS). (b) Weight gain. (c) Proctolin. Data show predicted means and s.e. at each week. Statistical significance is calculated between groups (**P<0.01 and ***P<0.001) and vs baseline (that is, 0; *CBD, **AMI; ***P<0.001, ****P<0.001).

Figure 4 Changes from baseline in fatty acid amide hydrolase substrates determined using mixed effects repeated measures model analysis (adjusted for baseline). (a) Anandamide (AEA) in serum. (b) Oxycteylethanolamide (OEA) in serum. (c) Palmitoylethanolamide (PEA) in serum. Data show predicted means and s.e. at each week. Statistical significance is calculated between groups (**P<0.01 and ***P<0.001) and vs baseline (that is, 0; *CBD, **AMI; ***P<0.001, ****P<0.001).
Figure 5  Association of change in anandamide in serum and change in the Positive and Negative Symptoms Scale total score in patients treated and observed per protocol. (a) Individual changes of patients treated with cannabidiol (n = 14). (b) Individual changes of patients treated with amisulpride (n = 8). P-values are from the Wilcoxon signed rank test of the null hypothesis that the distribution of slope is symmetric about zero.
CBD – Psychosis of Parkinson’s Disease

• Open-label non-blinded pilot study
  – (University Hospital Riberao Preto, Brazil)

• 6 outpatients – PD and psychosis x 3+months

• Pure CBD (99.9%) capsule (THC Pharm, Frankfurt, Germany)

• 4 weeks treatment 150→400mg/day

• Significant reduction in psychotic symptoms
  – Brief psychotic rating scale score 18→10→8→5.5  p<0.001
  – Clinical global impression improvement 4→2→1.5→1.5  p=0.001
    • 7=much worse  4=no change  1=very much improved

• No change in cognitive or motor function

• No significant side-effects noted

J Psychopharmacology November 21, 2008
Placebo-controlled study on CBD and public speaking anxiety in humans

Figure 2 Changes in SSPS-N scores induced by simulated public speaking test (SPST). Other specifications are in the legend of Figure 1. *Indicates significant differences from healthy control and + from social anxiety patients who received cannabidiol.
D9-Tetrahydrocannabinol (D9-THC) is the major psychoactive ingredient in cannabis. CBD is the major non-psychoactive ingredient in cannabis. Cannabis and D9-THC are anticonvulsant in most animal models but can be pro-convulsant in some healthy animals.

The psychotropic effects of D9-THC limit tolerability. CBD is anticonvulsant in many acute animal models, but there are limited data in chronic models.

The antiepileptic mechanisms of CBD are not known, but may include effects on the equilibrative nucleoside transporter; the orphan G-protein-coupled receptor GPR55; the transient receptor potential of vanilloid type-1 channel; the 5-HT1a receptor; and the a3 and a1 glycine receptors. CBD has neuro-protective and anti-inflammatory effects, and it appears to be well tolerated in humans, but small and methodologically limited studies of CBD in human epilepsy have been inconclusive.

More recent anecdotal reports of high-ratio CBD:D9-THC medical marijuana have claimed efficacy, but studies were not controlled.

CBD bears investigation in epilepsy and other neuropsychiatric disorders, including anxiety, schizophrenia, addiction, and neonatal hypoxic-ischemic encephalopathy. However, we lack data from well-powered double-blind randomized, controlled studies on the efficacy of pure CBD for any disorder.
Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter and
Department of Neurology, Stanford University

Catherine Jacobson
Department of Neurology, Stanford University

We found that parents of children with severe treatment-resistant epilepsies are using cannabidiol-enriched cannabis to treat their child’s epilepsy. Parents report a high rate of success in reducing seizure frequency with this treatment. Cannabidiol-enriched cannabis appears to be behaviorally well tolerated with some positive side effects not commonly associated with other AEDs. There are, of course, multiple limitations of an anonymous parental survey. We cannot verify the doses or the children’s response to the cannabidiol-enriched cannabis. We approached a group of parents who have an ongoing interest in using
Studies in Colorado using cannabis extracts to treat epilepsy in children

- Chapman et al. – University of Colorado – retrospective observation
- 58 children with catastrophic forms of epilepsy
- Treated with artisanal oral cannabis extracts
- 1/3 parents reported seizure reduction > 50%
- Families who moved to Colorado for CBD treatment were 3 times as likely to report reduction than families already in Colorado
- 2/16 had improvement in EEG compared to baseline EEG
- 47% had adverse reactions
  - Increase or new seizures in 21%
  - Somnolence fatigue in 14%
  - Developmental regression in 10%
- One intubation and one death
- “This substantial gap between the clinical observations and various anecdotal reports highlighted in the popular media underscores the desperate need shared by the entire epilepsy community for robust scientific evidence regarding the potential benefit and risks or marijuana in people with epilepsy.”  
  
  Kevin Chapman MD, Pediatric neurologist University of Colorado

Source: American Epilepsy Society Annual Meeting, Seattle WA, December 2014
Purified Cannabidiol (CBD) 98% (*Epidialex*) in addition to prescription medications for treatment of epilepsy

- NY University – Orrin Devinsky MD – professor of neurology
- 23 children – randomized clinical trial but not placebo controlled
- Severe epilepsy – Baseline AED – add CBD x 3 months
- 39% of patients >50% reduction in seizures
- Seizure-free - 3/9 Dravet patients
- Seizure free - 1/14 patients with other forms of epilepsy
- Mild adverse reactions including sleepiness, fatigue, change in appetite, diarrhea
- No deaths or reported increase in seizure frequency

Source: American Epilepsy Society Annual Meeting, Seattle WA, December 2014
What we **do not know** about Hemp extract oil and treatment of seizures

- Batch-to-batch composition
  - Potential harm due to withdrawal seizures when CBD content of extract oil is low
- Dosing regimen
- Drug-drug interactions
- Absorption studies
- Safety in pregnancy
- Long-term efficacy
  - Tolerance development
  - Down regulation of CBD receptors in the brain → uncertain consequences
Current studies at University of Utah using cannabinoids for treatment of epilepsy

1. Cannabidiol (CBD) “Epidialex” GW Pharmaceuticals
   • FDA-DEA-IRB Approved open label, phase I, multicenter trial
   • Started September 2014
   • 25 patients from Utah with uncontrolled seizures
   • >50% of kids show reduction in seizures
     – 1 child no seizures
     – there are side-effects - 17% mostly mild.
     – There was one child at another center with liver failure.
   • Next step - Double-blind controlled trial using CBD for Dravet Syndrome

2. “Hemp Oil” treatment of intractable epilepsy due to 2014 legislation
   – no data available yet but they are collecting data.

Edward B. Clark, MD  Department of Pediatrics, UUMC - Presentation to Utah HHS Interim Committee July 2015
• β-amyloid induces microglial activation in AD
• Microglial activation causes inflammation and damages the brain in AD
• CBD was tested in vitro and was shown to inhibit microglial activation.
• CBD also had a beneficial effect on learning in mice that had been injected with β-amyloid
• Authors suggest that CBD could be useful in treating and preventing AD in humans
Summary

• Cannabis plants in 2015 – high variability THC content with generally low CBD content
• High THC content associated with serious impairment, intoxication and negative mental health outcomes
• Children and adolescents are particularly vulnerable to negative short and long-term effects of cannabis
• Use of cannabis (smoked or ingested) with high THC and low CBD content causes public health problems
• Cannabis edibles are highly variable in their effects
• Smoking or eating the marijuana plant is not necessary or advisable for medicinal applications of useful cannabinoids
• CBD can block negative psychoactive effects of THC.
Summary

- Cannabidiol (CBD) may have significant potential for treatment and prevention of various diseases
- CBD does not appear to cause intoxication or present potential for abuse or addiction
- CBD does not appear to cause serious short or long-term side effects
- CBD blocks negative psychoactive effects of THC
- Hemp and other strains of Cannabis that have high levels of CBD and low levels of THC should be grown and processed in a controlled fashion so that they can be dosed in controlled clinical trials with predictable and reproducible content of CBD, THC and other cannabinoids.
- Legalization of personal backyard or basement growing of any type of Cannabis for medicinal use is *de facto* legalization of high THC low CBD Cannabis for recreational use because it is not possible to regulate or control cannabis under such circumstances.
Some Potential Uses of CBD

- Chronic pain management (neuropathic pain) - (may benefit from addition of THC)
- Pain and spasticity of multiple sclerosis — (may benefit from addition of THC)
- Cancer pain management - (may benefit from addition of THC)
- Certain types of epilepsy
- Nausea and wasting related to cancer, chemo, AIDS- (may benefit from addition of THC)
- Prevention of complications of diabetes
- Substance addiction treatment
- Treatment of some cancers (brain, breast, colon)
- Neurodegenerative diseases (Parkinson’s, Alzheimer’s, Huntington’s)
- Anxiety disorders
- Schizophrenia
- Inflammatory diseases
  - Rheumatoid arthritis and other autoimmune arthritis problems.
  - Crohn’s Disease
  - Ulcerative Colitis
Medicinal Cannabis Policy

• Use for specific conditions based on results of controlled studies – not anecdote.
• Protect children from accidental and deliberate access/overdose
• Additional clinical research is needed
• Changes in federal laws and regulations
• Use outside of the FDA/DEA rules?
• Compassionate use before FDA approval?
  – Hopeless conditions and/or terminal illness
• Regulation of plant production, processing and distribution?
  – State or contracted grower vs. private grower
  – Licensing and monitoring of people in the process
  – Specific stains – low THC high CBD Hemp vs. Cannabis Sativa with high CBD content
• Method of processing and administration?
  – Oil extracts vs. Edibles vs. Inhalers vs. E-cig vs. smoked joints
  – Whole plant preparations vs. specific purified extracts
• Effects and uses of other phytocannabinoids and metabolites besides CBD?
• Regulation of cannabinoid plants and content?
  – Testing of batches – certification of content → reliability of dosing?????
  – Development of pharmaceutical grade CBD and other cannabinoids
  – Monitoring for contaminants and adulteration
  – Plant-to-plant variability – growing conditions
  – CBD vs. THC - There are no studies that show that high CBD content interferes with any beneficial effect of THC
Figure 1. The endocannabinoid signaling system. CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; FAAH, fatty acid amide hydrolase; MGL, monoacylglycerol lipase; ABHD6, α-β hydrolase domain-containing protein 6; ABHD12, α-β hydrolase domain-containing protein 12; NAPE, N-arachidonoyl phosphatidylethanolamine; PE, phosphatidylethanolamine; PC, phospholipase C; PD, phospholipase D; DGL, diacylglycerol lipase; FABP, fatty-acid-binding protein; AEA, arachidonylethanolamide; 2-AG, 2-arachidonoylglycerol; ER, endoplasmic reticulum. Figure adapted from M. Nasr and A. Makriyannis, unpublished results.