USE OF ENDCANNABINOIDS IN CLINICAL PRACTICE

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AKASACARE INTEGRATIVE MEDICINE AND SURGERY
DISCLOSURES:

MEDICAL DIRECTOR AND CHIEF MEDICAL OFFICER, AMERICAN SHAMAN CBD
On April 20, 2018, Gov. Jeff Coyler, M.D. signed into law Senate Bill 263, which enacts the Alternative Crop Research Act. The law allows the Kansas Department of Agriculture (KDA) to oversee an industrial hemp program that gives the “opportunity to grow a new specialty oilseed crop in Kansas and offers potential for diversification for Kansas farmers looking for an alternative crop.” Under the law, individual licensed growers and those working with universities or other parties are able to grow hemp for research and development purposes.
SENATE BILL No. 263

An Act concerning industrial hemp; enacting the alternative crop research act; excluding industrial hemp from definition of marijuana and cannabinoids; amending K.S.A. 2017 Supp. 21-5701, 21-5702, 65-4101 and 65-4105 and repealing the existing sections.
Calendar No. 380

115th Congress
2d Session

S. 2667

To amend the Agricultural Marketing Act of 1946 to provide for State and Tribal regulation of hemp production, and for other purposes.

IN THE SENATE OF THE UNITED STATES

April 12, 2018

Mr. McConnell (for himself, Mr. Wyden, Mr. Merkley, and Mr. Paul) introduced the following bill; which was read the first time

April 16, 2018

Read the second time and placed on the calendar
ENOCANNABINOID (EC) SYSTEM

- Named after the marijuana plant *Cannabis sativa*
- Unique communications system in the brain and body
- Natural cannabinoids produced by the body interact with the EC system
CANNABINOIDS (CBD AND THC)

- Acts on cannabinoid receptors in cells that alter neurotransmitter release
- Cannabinoid receptors in brain AND entire body
- Produces many effects through multiple molecular pathways
## Table of Brain Structures and Their Functions

<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>Regulates</th>
<th>THC Effect on User</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>emotions, fear, anxiety</td>
<td>panic/paranoia</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>planning/starting a movement</td>
<td>slowed reaction time</td>
</tr>
<tr>
<td>Brain Stem</td>
<td>information between brain and spinal column</td>
<td>antinausea effects</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>motor coordination, balance</td>
<td>impaired coordination</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>learning new information</td>
<td>impaired memory</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>eating, sexual behavior</td>
<td>increased appetite</td>
</tr>
<tr>
<td>Neocortex</td>
<td>complex thinking, feeling, and movement</td>
<td>altered thinking, judgment, and sensation</td>
</tr>
<tr>
<td>Nucleus Accumbens</td>
<td>motivation and reward</td>
<td>euphoria (feeling good)</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>transmission of information between body and brain</td>
<td>altered pain sensitivity</td>
</tr>
</tbody>
</table>

The brain structures illustrated above all contain high numbers of CB receptors.
CANNABINOIDS (CBD AND THC)

CANNABINOID 1 RECEPTORS
  Found in brain and reproductive systems

CANNABINOID 2 RECEPTORS
  Found in immune system, greatest density in spleen
  Thought to be involved in anti-inflammatory effect
CANNABIDIOL (CBD)

1. Comes from hemp and marijuana plants.
2. Is non-psychoactive.
3. It is not marijuana.
4. Hemp plants can contain low levels of THC.
CANNABIDIOL (CBD)

• There are over one hundred types of cannabinoids.
• Acts as an indirect agonist to CB1 and CB2 receptors.
• Counteracts effects of THC.
• Found in stalks and leaves of plants.
Terpenes

- Over 200 identified
- Contribute to the flavor and scent of hemp and marijuana
- Affect how cannabinoids bind to receptors
Terpenoids are quite potent, and affect animal and even human behaviour when inhaled from ambient air at serum levels in the single digits ng·mL$^{-1}$. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Phyto cannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant *Staphylococcus aureus*).

CONCLUSION: Phytocannabinoid and terpenoid content offer complementary pharmacological activities that may strengthen and broaden clinical applications and improve the therapeutic index of cannabis extracts containing THC, or other base phytocannabinoids. Psychopharmacological and dermatological indications show the greatest promise.
THC

- TETRAHYDROCANNABINOL
- THE MOST PSYCHOACTIVE COMPONENT
- INCREASES GAMMA ACTIVITY IN THE BRAIN
- GIVES THE EUPHORIC EFFECT
- FOUND IN THE BUD OF THE PLANT
SYNTHETIC RX

- **DRONABINOL (MARINOL)/ Synthetic THC/Schedule III**
- **Indications:**
  - Anorexia Associated with Weight Loss in Adult Patients with AIDS
    - 2.5 mg orally twice daily, one hour before lunch and dinner
    - In elderly patients or patients unable to tolerate 2.5 mg twice daily, initiate at 2.5 mg once daily one hour before dinner or at bedtime to reduce the risk of central nervous system (CNS) symptoms
    - If tolerated and further therapeutic effect is desired, the dosage may be increased gradually to 2.5 mg one hour before lunch and 5 mg one hour before dinner
SYNTHETIC RX

- DRONABINOL (MARINOL)

  - Indications: (cont)
    - Anorexia Associated with Weight Loss in Adult Patients with AIDS (cont)
      - dose may be further increased to 5 mg one hour before lunch and 5 mg one hour before dinner, as tolerated to achieve a therapeutic effect
      - Maximum Dosage: 10 mg twice daily
      - Increase the dose of MARINOL gradually to avoid CNS affects
DRONABINOL (Marinol) (cont.)

Indications (cont.)

Nausea and Vomiting Associated with Cancer Chemotherapy in Adult Patients Who Failed Conventional Antiemetics

- recommended starting dosage is 5 mg/m2, orally administered 1 to 3 hours prior to the administration of chemotherapy and then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses per day
- elderly patients, consider initiating MARINOL at 2.5 mg/m2 once daily 1 to 3 hours prior to chemotherapy to reduce the risk of CNS symptoms
- Administer the first dose on an empty stomach at least 30 minutes before eating. Subsequent doses can be taken without regard to meals
- dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial response, as tolerated to achieve a clinical effect, in increments of 2.5 mg/m2
- maximum dosage is 15 mg/m2 per dose for 4 to 6 doses per day
NABILONE (CESAMET, CANEMES)
- ANALOG TO DRONABINOL
- SCHEDULE II
- INDICATIONS:
  - Treatment of refractory nausea and vomiting associated with cancer chemotherapy in patients who have failed to adequately respond to conventional antiemetic regimens
- DOSAGE: one to three hours prior to chemotherapy
  - ADULTS: 1 to 2 mg orally two to three times daily on days 1, 2, and 3.
  - PEDIATRIC:
    - <18 kg: 0.5 mg every 12 hours
    - 18 to 30 kg: 1 mg every 12 hours
    - >30 kg: 1 mg every 8 to 12 hours
    - Maximum dose: 0.06 mg/kg/day
SYNTHETIC RX

- RIMONABANT (ACOMPLIA)
  - SELECTIVE CB1 RECEPTOR INVERSE AGONIST
  - WAS STUDIED AS AN OBESITY DRUG AND FOR SMOKING CESSATION
  - SERIOUS PSYCHOLOGICAL ADVERSE EFFECTS, SUCH AS SUICIDALITY AND DEPRESSION LED TO THE EVENTUAL GLOBAL WITHDRAWAL OF RIMONABANT BY SANOFI-AVENTIS
NATURAL OTC CBD

- WITH AND WITHOUT THC
- DEPENDENT ON STATE LAWS
- KANSAS DOES NOT CURRENTLY ALLOW THC OF ANY PERCENTAGE
- MISSOURI ALLOWS UP TO 0.3%, WHICH IS VERY LOW
- MULTIPLE BRAND NAMES (ALPHABETICAL)/ MULTIPLE CONCENTRATIONS
  - AMERICAN SHAMAN – KANSAS CITY, MISSOURI / 300 – 900MG
  - CBDMD – CHARLOTTE, NORTH CAROLINA / 300 – 5000MG
  - CHARLOTTE’S WEB – DENVER, COLORADO / 200 – 1800MG
  - GREEN GORILLA- LOS ANGELES, CALIFORNIA/ 150- 7500MG
  - HEMPLUCID – OREM, UTAH / 250 - 1500MG
  - PURE SPECTRUM – EVERGREEN, COLORADO / 250 -3000MG
NATURAL OTC CBD

- HAS PRACTICAL CLINICAL APPLICATIONS
- BANE OF THE PHARMACEUTICAL INDUSTRY, DIRECTLY COMPETES
- MULTIPLE STUDIES SHOW ITS BENEFIT IN MANY DISEASE PROCESSES
- PRACTICAL APPLICATION CAN BE DIFFICULT DUE TO THE VARIED PRODUCTS AND HOW THEY ARE PRODUCED
- NO STANDARDIZED PROCESS IN MANUFACTURING
- PRODUCT CONTENT AND TESTING VERIFICATION DIFFICULT TO VERIFY.
- KEY IS TO RESEARCH A PRODUCT AND KNOW IT WELL
- CAN GENERATE ADDITIONAL REVENUE FOR YOUR PRACTICE
MODES OF ADMINISTRATION

- Smoke
- Tincture
- Cream
- Edible
- Spray
- Patch
- Vape
PATENT 6630507

- DEPARTMENT OF HEALTH AND HUMAN SERVICES
- CANNABINOIDS ARE ANTIOXIDANTS AND NEUROPROTECTANTS
- DOES NOT BIND TO NMDA RECEPTORS
- TO TREAT ISCHEMIC OR NEURODEGENERATIVE DISEASES
  - ISCHEMIC STROKE, TRAUMA
  - ALZHEIMERS, PARKINSONS, HIV DEMENTIA
  - AUTOIMMUNE DISEASES
  - MYOCARDIAL INFARCTION
- NO SIGNS OF TOXICITY OR SERIOUS SIDE EFFECTS HAVE BEEN OBSERVED FOLLOWING CHRONIC ADMINISTRATION OF CANNABIDIOL TO HEALTHY VOLUNTEERS (Cunha et al., Pharmacology 21: 175-185, 1980)
TREATABLE CONDITIONS:
- HIV/AIDS
- ALZHEIMERS
- ARTHRITIS
- ASTHMA
- CANCER
- CHRONIC PAIN
- CROHNS DISEASE
TREATABLE CONDITIONS:
- EPILEPSY
- GLAUCOMA
- MULTIPLE SCLEROSIS
- PTSD
- ANXIETY
- LEWY BODY DEMENTIA
- PARKINSONS
- HYPERTENSION
A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study

Khalid A. Jadoon,¹ Garry D. Tan,² and Saoirse E. O'Sullivan¹

This article has been cited by other articles in PMC.
A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study.

Jadoon KA¹, Tan GD², O’Sullivan SE¹.

Abstract

BACKGROUND: Cannabidiol (CBD) is a nonpsychoactive phytocannabinoid used in multiple sclerosis and intractable epilepsies. Preclinical studies show CBD has numerous cardiovascular benefits, including a reduced blood pressure (BP) response to stress. The aim of this study was to investigate if CBD reduces BP in humans.

METHODS: Nine healthy male volunteers were given 600 mg of CBD or placebo in a randomized, placebo-controlled, double-blind, crossover study. Cardiovascular parameters were monitored using a finometer and laser Doppler.

RESULTS: CBD reduced resting systolic BP (-6 mmHg; P < 0.05) and stroke volume (-8 ml; P < 0.05), with increased heart rate (HR) and maintained cardiac output. Subjects who had taken CBD had lower BP (-5 mmHg; P < 0.05, especially before and after stress), increased HR (+10 bpm; P < 0.01), decreased stroke volume (-13 ml; P < 0.01), and a blunted forearm skin blood flow response to isometric exercise. In response to cold stress, subjects who had taken CBD had blunted BP (-6 mmHg; P < 0.01) and increased HR (+7 bpm; P < 0.05), with lower total peripheral resistance.

CONCLUSIONS: This data shows that acute administration of CBD reduces resting BP and the BP increase to stress in humans, associated with increased HR. These hemodynamic changes should be considered for people taking CBD. Further research is required to establish whether CBD has a role in the treatment of cardiovascular disorders.

PMID: 28614793   PMCID: PMC5470879   DOI: 10.1172/jci.insight.93760
CBD AND HYPERTENSION-BLOOD PRESSURE MEDICATION INTERACTIONS

• BETA BLOCKERS

• Acebutolol (Sectral)  
  Atenolol (Tenormin)  
  Betaxolol (Kerlone, Betoptic)  
  Bisoprolol (Zebeta)  
  Esmolol (Brevibloc)  
  Nebivolol (Bystolic)  
  Metoprolol (Lopressor, Toprol-XL).  
  Carteolol (Ocupress)  
  Penbutolol (Levatol)  
  Pindolol (Visken).
CBD AND HYPERTENSION-BLOOD PRESSURE MEDICATION INTERACTIONS

### ACE INHIBITORS

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
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<tr>
<td>Pharex</td>
<td>Enalapril</td>
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<tr>
<td>Hypace</td>
<td>Enalapril</td>
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<tr>
<td>Tensoril</td>
<td>Captopril</td>
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<tr>
<td>Naprilate</td>
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<td>Ramipril</td>
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<tr>
<td>Accupril</td>
<td>Quinapril</td>
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</table>
CBD AND HYPERTENSION - DOSING

- RECOMMENDED CBD DOSING FOR INDIVIDUALS ON OTHER PRESCRIPTION BLOOD PRESSURE MEDICATIONS:
  - 10MG TO 40MG PER DAY, DIVIDED IN TWO DOSES
  - 40MG TO 60MG PER DAY, DIVIDED IN TWO DOSES MAY BE OF BENEFIT, BUT BEST DONE UNDER THE DIRECTION OF A PHYSICIAN
CBD AND HYPERTENSION - DOSING

• HELPFUL IN CASES OF REFACTORY HYPERTENSION
• CASES WITH POLY PHARMACY MAY BENEFIT
• AS THE DOSE OF CBD INCREASES, ATTEMPT TO DECREASE THE DOSAGE OF THE ANTIHYPERTENSIVE
• PATIENTS TO KEEP BP LOG
• FREQUENT FOLLOW UP
• MOST STUDIES SUGGEST THAT 40 TO 60 MILLIGRAMS OF CBD WILL NOT INTERFER WITH OTHER MEDS
CBD PROMISING MEDICINE IN BASAL GANGLIA DISORDERS
BR J PHARMACOLOGY, AUG., 2011, FERNANDEZ ET AL

- SLOWING DOWN PROGERESSION OF NUERODENGERATION IN PARKINSON AND HUNTINGTONS
- PROTECTS THE STRIATAL NEURONS FROM OXIDATIVE INJURY IN EXPERIMENTAL MODELS
CBD PROMISING MEDICINE IN BASAL GANGLIA DISORDERS
BR J PHARMACOLOGY, AUG., 2011, FERNANDEZ ET AL

THE PROTECTIVE EFFECT OF CBD MAY BE THROUGH MECHANISMS INDEPENDENT OF CB(1) OR CB(2) RECEPTORS AND INVOLVES THE CONTROL OF THE BODIES NATURAL ANTIOXIDANT DEFENCES.

AND/OR
CBD PROMISING MEDICINE IN BASAL GANGLIA DISORDERS
BR J PHARMACOLOGY, AUG., 2011, FERNANDEZ ET AL

- THERE MAY BE DIRECT ACTIVATION OF THE CB(2) RECEPTORS THAT LEAD TO SLOWER PROGRESSION OF THE NEURODEGENERATION IN BOTH DISORDERS

- CB(2) RECEPTORS HAVE BEEN IDENTIFIED IN THE HEALTHY BRAIN AND SUBPOPULATIONS OF NEURONS

- CB(2) RECEPTORS ARE UPREGULATED IN RESPONSE TO DAMAGING STIMULI AN IN PD AND HD
CBD PROMISING MEDICINE IN BASAL GANGLIA DISORDERS
BR J PHARMACOLOGY, AUG., 2011, FERNANDEZ ET AL

- THIS “UPREGULATION” LEADS TO INCREASED PROINFLAMMATORY FACTORS.

- CBD ACTS AS A CB(2) RECEPTOR AGONIST IN BOTH DISORDERS

- SUPPORTS THE IDEA THAT THE CANNABINOID SYSTEM BEHAVES AS AN ENDOGENOUS NEUROPROTECTIVE SYSTEM
CBD PROMISING MEDICINE IN BASAL GANGLIA DISORDERS
BR J PHARMACOLOGY, AUG., 2011, FERNANDEZ ET AL

CONCLUSIONS:
EVIDENCE SO FAR SUPPORTS THAT CBD HAS ANTIOXIDANT PROPERTIES
CBD CAN ACTIVATE CB(2) RECEPTORS ACTING AS AN ANTAGONIST TO NUEROTOXICITY
DESERVES FURTHER PROMPT CLINICAL EVALUATION
CBD FOR THE TREATMENT OF PSYCHOSIS IN PARKINSONS
J. PSYCHOPHARMACOLOGY, NOV 2009, ZUARDI, ET. AL.

SIX PATIENTS WITH PARKINSONS FOR >3 MONTHS RECEIVED CBD STARTING AT DOSES OF 150MG/DAY FOR 3 MONTHS

PSYCHOTIC S/S IMPROVED BASED ON THE BRIEF PSYCHIARTIC RATING SCALE AND ON THE PARKINSONS PSYCHOSIS QUESTIONNAIRE.
CBD FOR THE TREATMENT OF PSYCHOSIS IN PARKINSONS
J. OF PSYCHOPHARMACOLOGY, NOV 2009

• DECREASED THE TOTAL SCORES ON THE **UNIFIED PARKINSONS RATING SCALE**

• CBD DID NOT WORSEN THE MOTOR FUNCTION

• NO ADVERSE AFFECTS

• SUGGEST CBD MAY BE EFFECTIVE, SAFE AND WELL TOLERATED FOR TREATMENT OF PSYCHOSIS IN PARKINSONS.

• **ONE MUST CONSIDER OTHER MEDICATIONS THAT THE INDIVIDUAL MAY BE TAKING**
CBD MAY IMPROVE QUALITY OF LIFE MEASURES IN PARKINSONS
J. PSYCHOPHARMACOLOGY, NOV., 2014, CHAGAS, ET. AL.

• 21 PD PATIENTS WITHOUT DEMENTIA/PSYCH.

• 3 GROUPS TREATED WITH PLACEBO, CBD 75MG/DAY AND CBD 300MG/DAY

• THE GROUP TREATED WITH CBD 300MG/DAY HAD A STATISTICALLY SIGNIFICANT IMPROVEMENT IN THEIR WELL BEING AND QUALITY OF LIFE (PDQ-39 SCORE)
CBD MAY IMPROVE QUALITY OF LIFE MEASURES IN PARKINSONS
J. PSYCHOPHARMACOLOGY, NOV., 2014, CHAGAS, ET. AL

• CONCLUSIONS:
• POSSIBLE EFFECT OF CBD IMPROVING QUALITY OF LIFE MEASURES
• LARGER STUDIES NEEDED
Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors.

Xiong W¹, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, Guan Y, Pan HL, Ren K, Xu Y, Zhang L.

Abstract

Certain types of nonpsychoactive cannabinoids can potentiate glycine receptors (GlyRs), an important target for nociceptive regulation at the spinal level. However, little is known about the potential and mechanism of glycineergic cannabinoids for chronic pain treatment. We report that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the α3 GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors nor with their psychoactive side effects. NMR analysis reveals a direct interaction between CBD and S295 in the third transmembrane domain of purified α3 GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking the α3 GlyRs. Our findings suggest that the α3 GlyRs mediate glycineergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• While this study was an animal study, clinically inflammatory conditions have improved in patients with arthritic conditions.

• One could extrapolate that other inflammatory conditions such as sport or work related injuries could benefit by the anti-inflammatory properties of CBD
Cannabinoids in the management of difficult to treat pain.

Russo EB.

Author information

Abstract
This article reviews recent research on cannabinoid analgesia via the endocannabinoid system and non-receptor mechanisms, as well as randomized clinical trials employing cannabinoids in pain treatment. Tetrahydrocannabinol (THC, Marinol(R)) and nabilone (Cesamet(R)) are currently approved in the United States and other countries, but not for pain indications. Other synthetic cannabinoids, such as ajulemic acid, are in development. Crude herbal cannabis remains illegal in most jurisdictions but is also under investigation. Sativex(R), a cannabis derived oromucosal spray containing equal proportions of THC (partial CB(1) receptor agonist) and cannabidiol (CBD, a non-euphoriant, anti-inflammatory analgesic with CB(1) receptor antagonist and endocannabinoid modulating effects) was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Their adjunctive addition to the pharmacological armamentarium for treatment of pain shows great promise.

KEYWORDS: analgesia; cannabidiol; cannabinoids; multiple sclerosis; pain management; tetrahydrocannabinol
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• **Multiple Sclerosis:**
  • An autoimmune disorder.
  • The body's own immune system attacks and destroys the tissue that surrounds the nerves called the myelin.
  • Disrupts communication between the brain and other parts of the body.
  • First symptoms between the ages of 20 and 40.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• Multiple Sclerosis:
  • Initial symptom of MS is often blurred or double vision, red-green color distortion, or even blindness in one eye
  • Muscle weakness in their extremities and difficulty with coordination and balance
Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain.

Iskedjian M¹, Bereza R, Gordon A, Piwko C, Einhorn TR.

+ Author information

Abstract

OBJECTIVE: Debilitating pain, occurring in 50-70% of multiple sclerosis (MS) patients, is poorly understood and infrequently studied. We summarized efficacy and safety data of cannabinoid-based drugs for neuropathic pain.

DATA SOURCES: Studies were identified from Medline, Embase, and Cochrane databases; Bayer Healthcare provided additional trials.

STUDY SELECTION: Accepted were randomized, double-blinded placebo-controlled trials of cannabinoid-based treatments for MS-related/neuropathic pain in adults ≥ or = 18 years of age.

DATA EXTRACTION: Two reviewers identified studies and extracted data; a third adjudicated disagreements. Data included baseline and endpoint pain scores on visual analog or 11-point ordinal scales.

DATA SYNTHESIS: Of 18 articles and three randomized controlled trial (RCT) reports identified, 12 articles and two reports were rejected (9 = inappropriate disease or outcome, 1 = duplicate, 1 = review, and 1 = abstract); six accepted articles and one RCT-report involved 298 patients (222 treated, 76 placebo); four examined Sativex (a cannabinoid/delta-9-tetrahydrocannabinol (THC) buccal spray) (observations = 196), five cannabinoid (n = 41), and three dronabinol (n = 91). Homogeneity chi(2) values were non-significant, allowing data combination. Analyses focused on baseline-endpoint score differences. The cannabinoid/THC buccal spray decreased pain 1.7 +/- 0.7 points (p = 0.018), cannabinoid 1.5 +/- 0.7 (p = 0.044), dronabinol 1.5 +/- 0.6 (p = 0.013), and all cannabinoids pooled together 1.6 +/- 0.4 (p < 0.001). Placebo baseline-endpoint scores did not differ (0.8 +/- 0.4 points, p = 0.023). At endpoint, cannabinoids were superior to placebo by 0.8 +/- 0.3 points (p = 0.029). Dizziness was the most commonly observed adverse event in the cannabinoid/THC buccal spray arms (39 +/- 16%), across all cannabinoid treatments (32.5 +/- 16%) as well as in the placebo arms (10 +/- 4%).

CONCLUSION: Cannabinoids including the cannabinoid/THC buccal spray are effective in treating neuropathic pain in MS.

LIMITATIONS: This review was based on a small number of trials and patients. Pain related to MS was assumed to be similar to neuropathic
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

- **Schizophrenia**:  
  - A chronic and severe mental disorder  
  - Affects how a person thinks, feels, and behaves.  
  - Starts between ages 16 and 30  
  - Lose touch with reality: Hallucinations, Delusions, Thought Disorders (unusual or dysfunctional ways of thinking)  
  - Movement disorders (agitated body movements)
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• Bipolar disorder:
  • Sometimes referred to as manic-depressive disorder
  • Characterized by dramatic shifts in mood, energy, and activity levels
  • Affect a person’s ability to carry out day-to-day tasks.
  • These shifts in mood and energy levels are more severe than the normal ups and downs that are experienced by everyone.
A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation.

Zuardi AW¹, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, McGuire PK, Guimarães FS.

Author information

Abstract

Δ(9)-tetrahydrocannabinol (Δ(9)-THC) is the main compound of the Cannabis Sativa responsible for most of the effects of the plant. Another major constituent is cannabidiol (CBD), formerly regarded to be devoid of pharmacological activity. However, laboratory rodents and human studies have shown that this cannabinoid is able to prevent psychotic-like symptoms induced by high doses of Δ(9)-THC. Subsequent studies have demonstrated that CBD has antipsychotic effects as observed using animal models and in healthy volunteers. Thus, this article provides a critical review of the research evaluating antipsychotic potential of this cannabinoid. CBD appears to have pharmacological profile similar to that of atypical antipsychotic drugs as seem using behavioral and neurochemical techniques in animal models. Additionally, CBD prevented human experimental psychosis and was effective in open case reports and clinical trials in patients with schizophrenia with a remarkable safety profile. Moreover, fMRI results strongly suggest that the antipsychotic effects of CBD in relation to the psychotomimetic effects of Δ(9)-THC involve the striatum and temporal cortex that have been traditionally associated with psychosis. Although the mechanisms of the antipsychotic properties are still not fully understood, we propose a hypothesis that could have a heuristic value to inspire new studies. These results support the idea that CBD may be a future therapeutic option in psychosis, in general and in schizophrenia, in particular.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• **Anxiety**: People with anxiety disorders frequently have intense, excessive and persistent worry and fear about everyday situations.

• Can be debilitating. Make it difficult to hold a job.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• Anxiety:
  • Types: panic disorder, obsessive compulsive disorder, social anxiety disorder and post-traumatic stress disorder
  • Cannabidiol has shown to reduce anxiety
Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug.

[Article in English, Portuguese]
Schier AR, Ribeiro NP, Silva AC, Hallak JE, Crippa JA, Nardi AE, Zuardi AW.

Abstract

OBJECTIVES: To review and describe studies of the non-psychotomimetic constituent of Cannabis sativa, cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action.

METHOD: The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints.

RESULTS: Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder.

CONCLUSION: Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• **Epilepsy**: chronic disorder, the hallmark of which is recurrent, unprovoked seizures.

• **Types of seizures**: sudden surge of electrical activity in the brain
  • Absence seizures (formerly known as petit mal seizures)
  • Myoclonic seizures
  • Clonic seizures
  • Tonic seizures
  • Tonic-clonic seizures (formerly known as grand mal seizures)
  • Atonic seizures (drop attacks)
Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter and Catherine Jacobson

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 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 anti-epileptic 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
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• What this study showed:
• The average number of anti-epileptic drugs tried before using CBD cannabis was 12.
• Sixteen (84 percent) of the 19 parents reported a reduction in their child’s seizure frequency while taking CBD cannabis.
• Two (11 percent) reported complete seizure freedom
• Eight (42 percent) reported a greater than 80 percent reduction in seizure frequency
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• **What this study showed:**
  - six (32 percent) reported a 25–60 percent seizure reduction.
  - Other beneficial effects included increased alertness, better mood and improved sleep.
  - While side effects included drowsiness and fatigue.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• Cancer

• Several scientific reports demonstrate that CBD benefits include possessing antiproliferative, pro-apoptotic effects that inhibit cancer cell migration, adhesion and invasion.
Cannabidiol as potential anticancer drug

Paola Massi, Marta Solinas, Valentina Cinquina, and Daniela Parolaro

Abstract

Over the past years, several lines of evidence support an antitumourigenic effect of cannabinoids including Δ⁹-tetrahydrocannabinol (Δ⁹-THC), synthetic agonists, endocannabinoids and endocannabinoid transport or degradation inhibitors. Indeed, cannabinoids possess anti-proliferative and pro-apoptotic effects and they are known to interfere with tumour neovascularization, cancer cell migration, adhesion, invasion and metastasization. However, the clinical use of Δ⁹-THC and additional cannabinoid agonists is often limited by their unwanted psychoactive side effects, and for this reason interest in non-psychoactive cannabinoid compounds with structural affinity for Δ⁹-THC, such as cannabidiol (CBD), has substantially increased in recent years. The present review will focus on the efficacy of CBD in the modulation of different steps of tumourigenesis in several types of cancer and highlights the importance of exploring CBD/CBD analogues as alternative therapeutic agents.

Keywords: cancer cells, cannabidiol, invasion, metastasization, proliferation
• Cancer

• A 2006 study published in the Journal of Pharmacology and Experimental Therapeutics found for the first time that CBD potently and selectively inhibited the growth of different breast tumor cell lines and exhibited significantly less potency in non-cancer cells.
Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma.


Abstract
Delta(9)-Tetrahydrocannabinol (THC) exhibits antitumor effects on various cancer cell types, but its use in chemotherapy is limited by its psychotropic activity. We investigated the antitumor activities of other plant cannabinoids, i.e., cannabidiol, cannabigerol, cannabichromene, cannabidiol acid and THC acid, and assessed whether there is any advantage in using Cannabis extracts (enriched in either cannabidiol or THC) over pure cannabinoids. Results obtained in a panel of tumor cell lines clearly indicate that, of the five natural compounds tested, cannabidiol is the most potent inhibitor of cancer cell growth (IC(50) between 6.0 and 10.6 microM), with significantly lower potency in noncancer cells. The cannabidiol-rich extract was equipotent to cannabidiol, whereas cannabigerol and cannabichromene followed in the rank of potency. Both cannabidiol and the cannabidiol-rich extract inhibited the growth of xenograft tumors obtained by s.c. injection into athymic mice of human MDA-MB-231 breast carcinoma or rat v-K-ras-transformed thyroid epithelial cells and reduced lung metastases deriving from intrapaw injection of MDA-MB-231 cells. Judging from several experiments on its possible cellular and molecular mechanisms of action, we propose that cannabidiol lacks a unique mode of action in the cell lines investigated. At least for MDA-MB-231 cells, however, our experiments indicate that cannabidiol effect is due to its capability of inducing apoptosis via: direct or indirect activation of cannabinoid CB(2) and vanilloid transient receptor potential vanilloid type-1 receptors and cannabinoid/vanilloid receptor-independent elevation of intracellular Ca(2+)) and reactive oxygen species. Our data support the further testing of cannabidiol and cannabidiol-rich extracts for the potential treatment of cancer.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• In 2011, researchers added light on the cellular mechanism through which **CBD induces cell death in breast cancer cells**. They showed that CBD induced a concentration-dependent cell death of both estrogen receptor-positive and estrogen receptor-negative breast cancer cells.
Novel mechanism of cannabidiol-induced apoptosis in breast cancer cell lines.

Sultan AS¹, Marie MA², Sheweita SA³.

Abstract
Studies have emphasized an antineoplastic effect of the non-psychoactive, phyto-cannabinoid, Cannabidiol (CBD). However, the molecular mechanism underlying its antitumor activity is not fully elucidated. Herein, we have examined the effect of CBD on two different human breast cancer cell lines: the ER-positive, well differentiated, T-47D and the triple negative, poor differentiated, MDA-MB-231 cells. In both cell lines, CBD inhibited cell survival and induced apoptosis in a dose dependent manner as observed by MTT assay, morphological changes, DNA fragmentation and ELISA apoptosis assay. CBD-induced apoptosis was accompanied by down-regulation of mTOR, cyclin D1 and up-regulation and localization of PPARγ protein expression in the nuclei and cytoplasmic of the tested cells. The results suggest that CBD treatment induces an interplay among PPARγ, mTOR and cyclin D1 in favor of apoptosis induction in both ER-positive and triple negative breast cancer cells, proposing CBD as a useful treatment for different breast cancer subtypes.

KEYWORDS: Apoptosis; Breast cancer; Cannabidiol; Cyclin D1 and PPARγ; mTOR

PMID: 30007266 DOI: 10.1016/j.breast.2018.06.009
Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy.

Shrivastava A¹, Kuzontkoski PM, Groopman JE, Prasad A.

Abstract
Cannabidiol (CBD), a major nonpsychoactive constituent of cannabis, is considered an antineoplastic agent on the basis of its in vitro and in vivo activity against tumor cells. However, the exact molecular mechanism through which CBD mediates this activity is yet to be elucidated. Here, we have shown CBD-induced cell death of breast cancer cells, independent of cannabinoid and vallinoid receptor activation. Electron microscopy revealed morphologies consistent with the coexistence of autophagy and apoptosis. Western blot analysis confirmed these findings. We showed that CBD induces endoplasmic reticulum stress and, subsequently, inhibits AKT and mTOR signaling as shown by decreased levels of phosphorylated mTOR and 4EBP1, and cyclin D1. Analyzing further the cross-talk between the autophagic and apoptotic signaling pathways, we found that beclin1 plays a central role in the induction of CBD-mediated apoptosis in MDA-MB-231 breast cancer cells. Although CBD enhances the interaction between beclin1 and Vps34, it inhibits the association between beclin1 and Bcl-2. In addition, we showed that CBD reduces mitochondrial membrane potential, triggers the translocation of BID to the mitochondria, the release of cytochrome c to the cytosol, and, ultimately, the activation of the intrinsic apoptotic pathway in breast cancer cells. CBD increased the generation of reactive oxygen species (ROS), and ROS inhibition blocked the induction of apoptosis and autophagy. Our study revealed an intricate interplay between apoptosis and autophagy in CBD-treated breast cancer cells and highlighted the value of continued investigation into the potential use of CBD as an antineoplastic agent.

PMID: 21566064 DOI: 10.1158/1535-7163.MCT-10-1100
Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis.


Erratum in

Abstract
Invasion and metastasis of aggressive breast cancer cells are the final and fatal steps during cancer progression. Clinically, there are still limited therapeutic interventions for aggressive and metastatic breast cancers available. Therefore, effective, targeted, and non-toxic therapies are urgently required. Id-1, an inhibitor of basic helix-loop-helix transcription factors, has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. We previously reported that cannabidiol (CBD), a cannabinoid with a low toxicity profile, down-regulated Id-1 gene expression in aggressive human breast cancer cells in culture. Using cell proliferation and invasion assays, cell flow cytometry to examine cell cycle and the formation of reactive oxygen species, and Western analysis, we determined pathways leading to the down-regulation of Id-1 expression by CBD and consequently to the inhibition of the proliferative and invasive phenotype of human breast cancer cells. Then, using the mouse 4T1 mammary tumor cell line and the ranksum test, two different syngeneic models of tumor metastasis to the lungs were chosen to determine whether treatment with CBD would reduce metastasis in vivo. We show that CBD inhibits human breast cancer cell proliferation and invasion through differential modulation of the extracellular signal-regulated kinase (ERK) and reactive oxygen species (ROS) pathways, and that both pathways lead to down-regulation of Id-1 expression. Moreover, we demonstrate that CBD up-regulates the pro-differentiation factor, Id-2. Using immune competent mice, we then show that treatment with CBD significantly reduces primary tumor mass as well as the size and number of lung metastatic foci in two models of metastasis. Our data demonstrate the efficacy of CBD in pre-clinical models of breast cancer. The results have the potential to lead to the development of novel non-toxic compounds for the treatment of breast cancer metastasis, and the information gained from these experiments broaden our knowledge of both Id-1 and cannabinoid biology as it pertains to cancer progression.
MEDICAL CONDITIONS THAT CAN BENEFIT FROM CBD

• Data also suggests that CBD can be used to inhibit the invasion of lung and colon cancer, plus it possesses anti-tumor properties in gliomas and has been used to treat Leukemia.
Cannabinoids in the treatment of cancer

Cannabinoids are currently used in cancer patients to palliate wasting, emesis and pain that often accompany cancer. A significant advancement in cannabinoid use in cancer treatment came from the discovery of a potential utility of these compounds for targeting and killing cancer cells. In 1975 Munson et al. [17] demonstrated that the administration of $\Delta^9$-THC, $\Delta^8$-THC and cannabinol inhibited the growth of Lewis lung adenocarcinoma cells \textit{in vitro} as well as \textit{in vivo} after oral administration \textbf{in} mice. The interest in anticarcinogenic properties of cannabinoids was even renewed after the discovery of the eCB system and the cloning of the specific cannabinoid receptors. Since then, several cannabinoids have been shown to exert anti-proliferative and pro-apoptotic effects in various cancer types (lung, glioma, thyroid, lymphoma, skin, pancreas, uterus, breast, prostate and colorectal carcinoma) both \textit{in vitro} and \textit{in vivo}[18–26]. Moreover, other antitumourigenic mechanisms of cannabinoids are currently emerging, showing their ability to interfere with tumour neovascularization, cancer cell migration, adhesion, invasion and metastasization [27].
CBD and glioma

CBD also possesses anti-tumoural properties in gliomas, tumours of glial origin characterized by a high morphological and genetic heterogeneity and considered one of the most devastating neoplasms, showing high proliferative rate, aggressive invasiveness and insensitivity to radio- and chemotherapy.

After the seminal paper of Jacobsson et al. [36] demonstrating a serum-dependent effect of CBD upon C6 murine glioma cell proliferation, Massi et al. in 2004 [37] reported that CBD was effective in inhibiting U87-MG and U373 human glioma cell proliferation in vitro through the induction of apoptosis. Interestingly, CBD did not affect viability of non-transformed primary glial cells [38]. When tumour xenografts were generated in immune-deficient mice, in vivo intratumoural treatment with CBD significantly reduced tumour growth [37].
Among the cellular events involved in glioma cell death, CBD produced a time-dependent release of cytochrome C and activation of caspase-8, -9 and -3, suggesting the involvement of both the intrinsic and extrinsic apoptotic pathways [38]. Marcu et al. [39] later confirmed the efficacy of CBD in inhibiting the growth of multiple glioblastoma cell lines in a more potent way than Δ⁹-THC. Interestingly, combined treatment of Δ⁹-THC with CBD demonstrated that CBD enhanced the Δ⁹-THC inhibitory effect on glioblastoma cell growth, but not on invasiveness [39]. In line with this, more recently Torres et al. [40] confirmed that combined treatment with CBD and Δ⁹-THC greatly reduced human glioma cell viability
CONCLUSIONS

• CBD is a non-psychoactive, non-toxic compound.
• Studies show that doses of 700 milligrams per day for 6 weeks did not show any overt toxicity in humans.
• Can be used for prolonged treatment.
• Is not the same compound as marijuana (THC) and can be derived from hemp plants.
• Can legally be imported. $500 million dollars a year imported and growing.
CONCLUSIONS

• CBD benefits:
  • Effective in fighting breast cancer cells
  • Data also suggests that it can be used to inhibit the invasion of lung and colon cancer
  • Possesses anti-tumor properties in gliomas and has been used to treat
  • Decreases pain, inflammation, and spasm in conditions such as osteoarthritis and rheumatoid arthritis
  • May improve autoimmune conditions such as multiple sclerosis
CONCLUSIONS

• **CBD BENEFITS:**
  • Reduce anxiety
  • Stabilizes schizophrenia and bipolar disorder.
  • Improve PTSD
  • Decrease Seizure activity and decrease medications
  • Other conditions: Autism, Diabetes, Cardiovascular Disease