



# Arthritis (osteoarthritis and rheumatoid arthritis)

SEPTEMBER 2016

## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Osteoarthritis (OA) is a degenerative joint condition and it constitutes the most common form of arthritis. It is not a single disease or process; rather it is the outcome of a range of processes leading to pathological structural changes and symptoms in one or more synovial joints. It can develop without any known underlying cause (primary OA), or it can develop

secondary to other processes such as trauma, congenital, mechanical or local factors (for example obesity or hypermobility) or as a sequelae of other inflammatory arthritides (Dunkley 2012). OA is a major source of pain, function limitation, and disability (Felson 1998). The past two decades have brought substantial new insights into what OA is and how it progresses. While the characteristic pathologic feature of OA is hyaline articular cartilage loss, it is increasingly recognized that OA is a disease of the entire joint and that all structures are affected. Bone remodeling and attrition occur relatively early in the disease and fibrocartilage (examples: meniscus; labrum of hip joint) degeneration leads to changes in load distribution. Protrusions of new cartilage develop and ossify, leading to further damage. The synovium can become inflamed and, as it swells, causes a spinal reflex, inhibiting complete activation of muscles that stabilize the joint. This, combined with lack of use, leads to muscle weakness and atrophy. The inflamed synovium triggers changes in the peripheral nervous system, affecting the afferent processing of pain signals from the joint and the surrounding tissues. A major driver of the development of the disease and its progression is aberrant loading of the joint. As the joint starts to display damage from the loading by way of cartilage erosion or ligament injury, loading becomes even more aberrant, setting up a cycle of increasing damage and symptoms. Pain and joint instability are the characteristic symptoms of OA. Early in the disease pain comes on with certain activities or actions of the joint, but later pain becomes more constant – probably indicating the development of a central sensitization of the pain. Changes in pain and function appear to have little relation to the trajectory of structural progression. What produces this variety in disease trajectory is not clear (Felson 2009).

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation and swelling of the joint synovium (linings), autoantibody production, cartilage and bone destruction, and systemic features including cardiovascular, pulmonary, psychological, and skeletal disorders (McInness 2011). Its cause is unknown, but there appears to be an inherited risk, as well as increased risk from several environmental and infectious exposures (McInness 2011). RA causes significant disability (Pincus 1984) and impairment of quality of life (Salaffi 2009) and reduces lifespan (Soloman 2003).

## Prevalence

Osteoarthritis is the most common form of arthritis. Symptomatic knee OA affects roughly 12% of persons 60 years old or older (Felson 1998). Rheumatoid arthritis affects 0.5-1% of the adult population (Helmick 2008). It can occur at any age, but most often it develops between the ages of 40-50 and its prevalence in women is three times that in men (Dunkley 2012).

## Current Therapies

Currently, OA treatment is symptomatic, targeting pain and inflammation and promoting rehabilitation. Acetaminophen (Tylenol) can be effective at relieving pain early in OA, but non-steroidal anti-inflammatory drugs and COX-2 inhibitors are often used for pain and inflammation reduction. Many of these drugs carry risk of cardiovascular and gastrointestinal

disease, however, when used long-term. Physical therapy can help reduce pain and maintain mobility, muscle strength and biomechanical integrity of the joint. Rehabilitative approaches to osteoarthritis include bracing or taping the affected joints, orthotic shoes, and exercise; in general they have modest effect on pain reduction (Felson 2009). In advanced disease with joint failure (disabling joint pain and loss of joint function and deformity) management is surgical with joint replacements (Dunkley 2012). There is hope that future disease-modifying medical therapies targeted at underlying pathological processes will become available, but currently treatment is symptomatic (Dunkley 2012).

The current approach to rheumatoid arthritis treatment is to begin therapy as soon as possible after diagnosis, with zero tolerance for inflammation and the goal of achieving clinical remission. Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine, sulpha-salazine, and lefunomide are started early and in combination. If inflammation continues, biologic drugs including anti-tumor necrosis factor drugs, B-cell depletion therapy, and anti-interleukin drugs or inhibitors to co-stimulatory molecules are started within 3-6 months of onset – usually concurrently with at least one of the DMARDs. Drugs used to treat RA have a wide variety of often serious side effects, with the biologic agents putting patients at increased risk of infections. Physical therapy and occupational therapy are important adjuncts to pharmacological treatment (Dunkley 2012). Existing treatments are not optimally effective, sometimes producing no remission or only partial remission. Sustained remission is rarely achieved and requires ongoing therapy (McInness 2011).

## Pre-Clinical Research

Numerous studies have been published regarding presence of cannabinoid receptors and endocannabinoids in the joints of humans with OA and RA and studies testing impact of synthetic cannabinoids and endocannabinoid modulators on rodents with research models of OA and RA. Articles described below are representative. Those who want to explore this area in more detail can identify additional articles in the Background and Discussion sections of these articles.

### *Presence of CB1 and CB2 receptors in OA and RA*

**Richardson D, Pearson RG, Kurian N, Larif ML, Garle MJ, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Research & Therapy* 2008, 10:R43 (doi:10.1186/ar2401)**

Inflamed synovial tissue and synovial fluid were obtained from 13 RA patients and 32 OA patients undergoing total knee arthroplasty and synovial fluid was obtained from 6 normal volunteers. The investigators found evidence that CB1 and CB2 receptors are present in the synovial tissue of RA and OA patients. The endocannabinoids AEA and 2-AG were found in the synovial fluid of RA and OA patients, but not in synovial fluid of healthy volunteers, giving support to the concept of endocannabinoid system involvement within the joints of RA and OA patients.

## Osteoarthritis

**Schuelert N, Johnson MP, Oskins JL, Jassal K, et al. Local application of the endocannabinoid hydrolysis inhibitor URB597 reduces nociception in spontaneous and chemically induced models of osteoarthritis. *Pain* 2011;152:975-981.**

This study tested the impact of enhancing endogenous cannabinoid levels within the arthritic joint in two rodent models of OA: rats with chemically-induced OA and guinea pigs with naturally-occurring OA. An inhibitor of FAAH, an enzyme that breaks down endocannabinoids, was injected into an artery proximal to an arthritic joint. The injection resulted in decreased firing of pain nerve fibers when the joint was hyper-rotated. Behavioral experiments carried out on the rats showed a beneficial effect of the injection. The amount of weight rats were willing to bear on their hind limbs decreased after induction of OA; subsequent injection of the FAAH inhibitor reduced the amount of hind-limb incapacitation.

**Schuelert N, McDougall JJ. Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. *Arthritis & Rheumatism* 2008;58:145-153.**

A rat model of OA was used to test the effect of a synthetic, selective CB1 agonist, ACEA. Injection of ACEA into the arthritic joint reduced firing of pain nerve fibers when the joint was hyper-rotated.

## Rheumatoid Arthritis

**Cox ML, Haller VL, Welch SP. Synergy between  $\Delta^9$ -tetrahydrocannabinol and morphine in the arthritic rat. *Eur J Pharm* 2007;567:125-130.**

The effects of morphine and THC, separately and in combination, were tested in a rat model of inflammatory arthritis. The model involves administering a killed mycobacterium preparation (Freund's complete adjuvant) into the skin, which results in a generalized inflammatory arthritis. Drug effect was measured by the paw pressure test. In this test the rat's hind paw is exposed to increasing mechanical pressure. The pressure at which the rat withdraws its limb is defined as the pain pressure threshold. A higher threshold is interpreted as a reduction in pain. In this study THC and morphine were found to have a synergistic interaction in pain reduction in both normal rats and the arthritic-model rats.

**Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of  $\Delta^9$ -tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* 1998;1:183-191.**

The effect of THC and the endocannabinoid anandamide were tested separately in a rat model of arthritis similar to the model used in Cox 2007. The investigators found that both THC and anandamide reduced pain in normal rats and had a similar pain-reducing effect in arthritic rats. Exploration of impact of a CB1 receptor antagonist showed different results for THC and for anandamide in pain reduction: pain reduction of THC was reduced, but there was no change in

pain reduction for anandamide. And naloxone blocked the pain reducing effect of both THC and anandamide. These findings led the authors to conclude, “This study indicates that anandamide and THC may act at different receptor sites to modulate endogenous opioid levels in mechanical nociception.”

**Krustev E, Reid A, McDougall JJ. Tapping into the endocannabinoid system to ameliorate acute inflammatory flares and associated pain in mouse knee joints. *Arthritis Research & Therapy* 2014, 16:437**

The effect of a synthetic inhibitor (URB597) of an enzyme (FAAH) that degrades the endocannabinoid anandamide was tested using a mouse model of inflammatory arthritis. Inhibition of the enzyme results in higher levels of anandamide. Anandamide has anti-inflammatory and analgesic qualities, and it was hypothesized that local administration of URB597 would result in evidence of decreased joint inflammation and pain. The mouse model of inflammatory arthritis was created by injecting an irritating substance (kaolin and carrageenan) into the mouse’s right knee joint. White blood cell adherence and blood flow within the joint were measures of inflammation. Hind limb weight bearing and sensitivity to hair filament testing were measures of pain. Hallmarks of decreased inflammation, decreased white blood cell rolling and decreased hyperemia were seen with low doses of URB597, but not with high doses. And injection of URB597 improved both hind limb weight bearing and the hair withdrawal thresholds. This led the authors to conclude, “These results suggest that the endocannabinoid system of the joint can be harnessed to decrease acute inflammatory reactions and the concomitant pain associated with these episodes.”

**Fukuda S, Kohsaka H, Takayasu A, Yokoyama W, et al. Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. *BMC Musculoskeletal Disorders* 2014, 15:275.**

This article describes both studies done on mice and studies done on human tissues.

1. A selective CB2 receptor agonist (JWH133) was tested on mice with murine-model rheumatoid arthritis. Use of JWH133, injected intraperitoneally, resulted in less synovial inflammation and bone destruction than in control mice.
2. CB2 receptor density was found to be higher in humans with RA than in humans with OA.
3. Fibroblast-like synovial cells from human RA synovium were cultured and then stimulated with a chemical that stimulates production of inflammatory mediators. Co-administration of JWH133 was found to dose-dependently suppress production of the inflammatory mediators.

## Clinical Trials

Two clinical trials of a cannabinoid for treatment of arthritis patients were found and are summarized below. In addition, ClinicalTrials.gov lists one trial (NCT02324777), a

randomized double-blind placebo-controlled, proof-of-concept crossover trial of vaporized cannabis in adults with painful osteoarthritis of the knee. 40 adults age  $\geq 50$  with primary OA will be recruited at two Canadian centers. Participant response will be assessed at a variety of time points (0 to 180 minutes) after inhaling vaporized cannabis of different THC/CBD ratios. Primary outcome measure is pain reduction. Secondary measures include functional outcomes; pharmacokinetic measures of plasma cannabinoid metabolites; changes in blood pressure, heart rate, hematocrit, renal function, liver enzymes; psychoactive adverse events, and global rating of preference for each cannabis preparation. Estimated date of completion is May, 2016.

**Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 2006;45(1):50-52.**

This was a double-blind, randomized, placebo-controlled study carried out for five weeks in patients diagnosed with rheumatoid arthritis (RA) on a stable regimen of traditional therapy but who did not gain adequate pain relief from standard treatments. A total of 58 participants (12 male/46 female; average age 62.8 years) met the inclusion criteria and 31 were randomized to treatment, while 27 received placebo. The patients were instructed to limit use to evening dosing to prevent daytime intoxication from the Sativex oral spray (2.7 mg THC/2.5 mg CBD per 100  $\mu$ l actuation[spray]) that was used throughout the trial. The titration schedule was one actuation before bed and increase by one actuation every two days, based on patient response, up to a maximum of six actuations per night.

The primary endpoint tested was based on a 0-10 pain scale assessing pain upon movement each morning and comparing the baseline rating to the average of the last 14 days of the trial. Secondary outcomes were pain at rest, sleep quality, morning stiffness, the Short Form McGill Pain Questionnaire (SF-MPQ), and the 28-Joint Disease Activity score (DAS28). All outcomes except morning stiffness and SF-MPQ intensity showed a statistically significant improvement when compared to placebo, including the SF-MPQ "pain at present" rating. Side effects were approximately twice as common in the active treatment group than in the placebo group. All but two of the side effects in the active treatment group were mild or moderate; two patients rated side effects as severe (constipation, malaise). The side effects more common in the active treatment group than in the placebo group were mild dizziness, dry mouth, light-headedness and fall. Three patients withdrew from the study because of side effects – all 3 from the placebo group. There were no serious adverse events in the active treatment group and two in the placebo group.

A recent Cochrane Review of neuromodulators for pain management in rheumatoid arthritis (Richards 2012) includes the Blake 2006 study and provides detailed discussion of its strengths and weaknesses. The authors conclude there is weak evidence that oromucosal cannabis is superior to placebo in reducing pain in patients with RA, but that the potential harms from side effects outweigh any modest benefits achieved.

**Higgins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomized, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-**

**04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* 2012;153:1837-1846.**

This randomized, double-blind, cross-over study assessed the effect of an FAAH inhibitor on pain in a human population with osteoarthritis. FAAH is an enzyme that metabolizes the endocannabinoid anandamide. Inhibition of FAAH was hypothesized to lead to increased levels of anandamide and related compounds and result in pain reduction, as has been observed in animal models of OA. 74 patients with OA were recruited and randomized into either the arm receiving PF-04457845 or the arm receiving Naproxen, the standard of care for treating OA symptoms. The trial involved 2 two-week treatment periods separated by a 2-week washout interval. In double-blind fashion, patients received active treatment in one of the treatment periods and placebo in the other. The Naproxen arm was carried out to test the validity of the washout period. Despite evidence of potent inhibition of FAAH and increase in endocannabinoid precursors, patients in the PF-04457845 group showed no difference in pain reduction with active treatment, compared to placebo, and the study was stopped at the interim analysis for futility.

## Observational Studies

No published observational studies were found related to use of cannabis or cannabinoids as therapy for pain or other symptoms in patients with osteoarthritis or rheumatoid arthritis. There are however, many testimonials and accounts of benefits from use of cannabis in RA and OA patients on web sites maintained by individuals and by organizations.

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the treatment of osteoarthritis or rheumatoid arthritis were found.

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Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomized, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* 2012;153:1837-1846.

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Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303-1307.

ISSUE BRIEF

Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Autism Spectrum Disorder (ASD)

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## Introduction

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Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by sustained social impairments in reciprocal social communication and interactions; and repetitive behaviors, interests, or activities (American Psychiatric Association 2013). These essential markers of autism spectrum disorder present in early childhood and limit everyday functioning (American Psychiatric Association 2013). The word "spectrum" is used to define ASD since the disorder manifests itself in diverse ways, depending on varying symptom severity,

the individual's developmental level, and chronological age (American Psychiatric Association 2013).

The Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the 2013 update to the American Psychiatric Association's classification and diagnostic tool. In the U.S. the DSM serves as the primary authority for psychiatric diagnosis. In the latest version of the DSM, several disorders have now been incorporated into the ASD definition, such as Kanner's autism and Asperger's disorder, among others (American Psychiatric Association, 2013). To be diagnosed with ASD, a person needs to fulfil the following criteria (American Psychiatric Association, 2013):

1. Persistent deficits in social communication and interaction across multiple contexts, as demonstrated by all of the following:
  1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and inability to have normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
  2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
  3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
  4. (These criteria can be currently occurring or have occurred in the patient's past. Examples are illustrative, not exhaustive.)
2. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following:
  1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., repetitive hand flapping, lining up toys or flipping objects, delayed or immediate parroting of others' speech, idiosyncratic phrases).
  2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
  3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., a child who is extremely attached to a spoon, an adult who spends hours rewriting specific phrases).
  4. Extremely exaggerated or dulled reactions to sensations or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
  5. (These criteria can be currently occurring or have occurred in the patient's past. Examples are illustrative, not exhaustive.)

3. Symptoms must be present in the early developmental period. Though, symptoms may not become fully apparent until social demands exceed limited capacities. Symptoms may also be masked by learned strategies in later life.
4. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
5. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur. Social communication should be below what is expected for general developmental level, in order to make comorbid diagnoses of autism spectrum disorder and intellectual disability.

## Prevalence

The Centers for Disease Control and Prevention estimates that 1 out of every 68 children in the United States has autism spectrum disorder (Christensen, 2016). ASD is roughly 4.5 times more common among boys than girls (Christensen, 2016). Since 2006, the prevalence of childhood ASD has increased by 23%, becoming a major public-health concern (Harrington and Allen, 2014). This increase in prevalence can be attributed to better screening and the DSM-5's broader definition of ASD, among other issues (Harrington and Allen, 2014).

Among both children and adults, roughly 3.5 million Americans live with autism spectrum disorder. Annually, costs associated with children who have ASD are \$61 billion in the United States. Adults living with ASD cost the U.S. \$196 billion per year (Buescher et al., 2014).

## Current Therapies

Several behavioral, educational, and pharmaceutical treatments exist to treat ASD (Harrington and Allen, 2014; Ospina et al., 2008). Pharmaceutical treatments mostly target comorbid health problems, which are common in children living with ASD (McPheeters et al., 2011).

Behavioral and developmental interventions are the primary treatments for ASD (Ospina et al., 2008). There is a great variety in the kinds of behavioral and developmental interventions, which are organized into smaller subcategories (Ospina et al., 2008). For example, within the continuum of behavioral and developmental interventions, applied behavioral analysis (ABA) is designed to teach socially appropriate behaviors and to decrease challenging behaviors (Harrington and Allen, 2014; Ospina et al., 2008). Another kind of behavior and developmental intervention is social skills training (SST), which targets social deficits (White and Koenig, 2007).

ABA-based therapies have demonstrated positive effects on language, adaptive, cognitive, and educational outcomes (Hanley, Iwata, & Thompson, 2001; Lovaas, 1987; Warren et al., 2011). However, there is a lack of high-quality randomized controlled trials (Warren et al., 2011). The studies that do evaluate behavioral and developmental interventions are

methodologically weak, include few participants, and do not evaluate long-term effects of interventions (Ospina et al., 2008). Therefore, the evidence to determine which behavioral interventions are most effective in children with ASD is inadequate (Warren et al., 2011). Studies on SST interventions are similarly low-quality, though evidence from several small, initial studies indicate that SST is potentially beneficial to children with ASD (White and Koenig, 2007).

Common comorbidities in children with ASD include intellectual disability, constipation, sleep disorders, anxiety, ADHD, and seizure disorders (Harrington and Allen, 2014; McPheeters et al., 2011). Treating comorbid mental-health issues in children with ASD is more challenging than treating common medical problems, such as constipation and sleep problems (Harrington and Allen, 2014). Antipsychotic medications, serotonin-reuptake inhibitors, and stimulants are among the pharmaceuticals used to treat mental-health comorbidities (McPheeters et al., 2011). However, despite the fact that medications are used to treat many children with ASD, there is little evidence to indicate that these pharmaceuticals are effective (McPheeters et al., 2011). Drugs that do demonstrate benefits for challenging or repetitive behaviors, are unfortunately associated with adverse effects, limiting their use to patients with severe impairments or risk of injury (McPheeters et al., 2011).

Turning to adolescents and young adults with ASD, studies examining the effectiveness of behavioral, pharmaceutical, and other therapies in this population are poor-quality (Taylor et al., 2012). There is a dramatic lack of evidence on the best way to treat adolescents and young adults who have ASD (Dove et al., 2012; Taylor et al., 2012).

## Pre-Clinical Research

Few pre-clinical research publications focusing on the endocannabinoid system and aspects of the neurologic system specific to ASD were found – perhaps because so little is known about the causes of ASD. The following publication reports on studies of mice with the Fragile X gene mutation. Fragile X syndrome in humans is the most commonly known genetic cause of autism.

**Jung KM, Sepers M, Henstridge, Lassalle, et al. Uncoupling of the endocannabinoid signaling complex in a mouse model of fragile X syndrome. *Nature Communications* 2012;3:1080 doi: 10.1038/ncomms2045.**

This highly technical article presents three lines of experimental evidence suggesting the protein missing because of the Fragile X gene mutation, FMRP, is required for normal operations of the endocannabinoid system. Specifically, FMRP appears to be necessary for normal production and release of 2-AG, an endocannabinoid considered important for brain development and functioning.

## Clinical Trials

No randomized, controlled clinical trials have been completed for cannabis product therapies and ASD and none underdevelopment were found on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Though internet blogs and discussion forums have numerous accounts of use of cannabis and cannabinoids in persons with autism, the following case history was the only publication found for therapeutic use of a cannabinoid or cannabis product for autism.

**Kurz, R., & Blaas, K. (2010). Use of dronabinol (delta-9-THC) in autism: a prospective single-case-study with an early infantile autistic child. *Cannabinoids*, 5(4), 4-6.**

In this study, purified delta-9-THC (dronabinol) was studied as a supplemental therapy in an autistic Austrian child. The child at the center of this study was diagnosed with early infantile autism at the age of three. He was six years old when the study was conducted. The study lasted six months.

During the study period, the child initially received dronabinol drops at a dosage of one drop every morning (0.62 mg THC). On a day-to-day basis, the dosage was gradually increased, reaching a maximum tolerated dose of 3.62 mg THC per day (two drops in the morning, one drop at midday, and three evening drops).

At the end of the six months, the boy's symptom severity significantly decreased in five different categories: hyperactivity, lethargy, irritability, stereotypic behavior, and inappropriate speech.

Based on these findings, the authors argue that dronabinol may be a therapeutic for treating early infantile autism. Dronabinol may not replace other therapies, but it is a potential, additional therapy. Larger, controlled studies on cannabinoids and autism are needed to further understand their findings, say the authors.

## Observational Studies

**De Alwis, D., Agrawal, A., Reiersen, A. M., Constantino, J. N., Henders, A., Martin, N. G., & Lynskey, M. T. (2014). ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. *Journal of studies on alcohol and drugs*, 75(2), 211-221.**

Substance use among people with autism spectrum disorders (ASD) is hypothesized to be rare, since those with ASD lack the social skills that would bring them into contact with others who use drugs and since people with ASD have less novelty-seeking behaviors than average. However, there are few studies to test this hypothesis. This study uses a cross-sectional interview and self-reported questionnaire to elucidate the relationship between people with autism traits, substance use, and substance abuse.

The interview and questionnaire's study sample size was 3,028 white, Australian twins born between 1972 and 1979. The study participants' drug use, abuse, and misuse were assessed through the interview. The self-reported questionnaire collected data on the participants' autistic traits.

Surprisingly, the results of the analysis indicate that cannabis use is associated with having autistic traits in a statistically significant manner. Cannabis abuse/dependence were also significantly associated with high levels of autistic traits.

Several factors limit interpretation of this finding, however. From a demographic perspective, the study sample is racially homogenous, and its findings may not be replicated in more diverse study samples. Causal relationships cannot be determined because of the study's cross-sectional design. Last, formal diagnostic criteria were not used to determine an autism spectrum disorder diagnosis: only autistic traits were studied.

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of autism spectrum disorder were found.

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN (zip) 55164-0882  
(phone) 651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Treatment-Resistant Depression

AUGUST 2016

## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Treatment-resistant depression (TRD) is somewhat difficult to define due to a lack of consensus on how to operationally define it. At a minimum, TRD is defined as an inadequate response to at least one antidepressant for adequate dosing and duration in treating major depressive disorder (Fava 2003; Berlim 2007), but in practice, it appears that it is more commonly defined as lack of adequate response to at least two different classes of antidepressant medications for adequate dosing and duration (Berlim 2007). Since TRD applies

to a subset of individuals with major depressive disorder (MDD), the following sentences describe MDD diagnosis.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association 2013) is the current authoritative tool for classifying and diagnosing MDD. The following criteria (A-E) are outlined verbatim from the DSM-5 for the diagnosis of MDD, with criteria A-C representing a major depressive episode (MDE).

Criterion A – Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation.)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Criterion B – The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Criterion C – The episode is not attributable to the physiological effects of a substance or to another medical condition.

Criterion D – The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

Criterion E – There has never been a manic episode or a hypomanic episode.

## Prevalence

Estimates from the National Comorbidity Survey Replication study indicates a national lifetime prevalence of MDD in adults to be at 16.2% (Kessler et al. 2003) which, as of July 2015 population estimates (US Census Bureau) translates into more than 40.1 million US adults having had MDD sometime in their lifetime. Data from the same study also indicated that 6.6% of adults suffered from MDD in the last 12-months which, as of 2015 US Census Bureau estimates, affects approximately 16.3 million US adults. Of those experiencing MDD, 50-60% are estimated to not achieve adequate response to at least one 8-week antidepressant trial (Fava et al. 2003; Rush et al. 2006).

## Current Therapies

According to the American Psychiatric Association's Practice Guideline for Treatment of Patients with Major Depressive Disorder, 3rd Edition (2010), both pharmacologic and non-pharmacologic therapies are used on MDD patients and, by extension, TRD patients. A combination of both pharmacologic and non-pharmacologic therapies may be recommended by clinicians depending on observed clinical features. A patient's initial preferences for treatment and any prior experiences with former treatment is also considered when developing a treatment plan. The following paragraphs in this section will discuss both pharmacologic and non-pharmacologic treatments that have targeted MDD patients in situations where comparative efficacy was ascertained or when TRD patients were specifically followed in the course of treatment. Lastly, it is important to introduce typical efficacy measures for MDD treatments: remission and treatment response. Remission in the literature refers to clinical absence of depressive symptoms (typically represented as a score below a set threshold to reflect clinical absence), while response typically refers to achieving at least a 50% reduction in depressive symptoms compared to baseline measures.

### Pharmacologic Treatments

Clinical practice guidelines overwhelmingly agree with the use of antidepressants as the first line of pharmacotherapy for MDD patients (APA 2010), with many patients starting on one of the following medications before moving onto other pharmacologic options: a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion. When patients do not show signs of remission or do not respond adequately to initial treatment, typical strategies in clinical practice are to switch (discontinue current treatment and switch to another antidepressant within the same class or in a different

class), combine (add another antidepressant on top of the current antidepressant treatment, or augment (add a non-antidepressant medication on top of current antidepressant treatment).

The National Institute of Mental Health (NIMH) funded the largest and longest running prospective study on depression treatment trials in primary and specialty care settings (Sequenced Treatment Alternatives to Relieve Depression; STAR\*D) in patients who did not show remission of depressive symptoms to initial antidepressant treatment. This particular study was designed to reflect typical treatment course found in clinical practice, which allowed for high generalizability of results in actual clinical practice. MDD patients already receiving care in an outpatient setting (both primary and specialty care clinics) were allowed to participate in this study. Patients who did not experience remission with the initial antidepressant treatment (citalopram; Level 1 treatment) or found the treatment intolerable were given the opportunity to continue onto other treatment strategies (sequentially from Level 2-Level 4), which involved switching to or combining/augmenting with another antidepressant or other drugs thought to enhance antidepressant response. Patients at each Level of progression indicated which treatment options they would be amenable to trying among a specified selection list, and their selections were used to randomly assign participants to one of those options. With each Level progression, clinicians increasingly dealt with patients with greater treatment resistance (patients achieving remission did not go onto the next Level within the study, as the intended outcome was achieved).

Results from the Level 1 trial (citalopram) showed a 28-33% remission rate in MDD patients, with the majority achieving remission by the 7th week of treatment. In addition, roughly 9% reported citalopram as intolerable (Trivedi et al. 2006). Patients who continued to Level 2 treatment (those not achieving remission or finding the Level 1 trial intolerable) were given the option to switch to another antidepressant or combine citalopram with another antidepressant. Patients selecting the switch option were randomly assigned to be prescribed either within-class sertraline or another antidepressant of another class (bupropion-SR or venlafaxine-XR; Rush et al. 2006). Patients selecting to combine for the Level 2 trial were randomly assigned to combine either bupropion-SR or buspirone with citalopram (Thase et al. 2007). Those who switched treatment for Level 2 had remission rates that were comparable across all three antidepressants at roughly 25%, with most achieving remission within 5-6 weeks (Rush et al. 2006). Those combining citalopram with another antidepressant showed slightly higher rates of remission (~30%) compared to the switching strategy (Thase et al. 2007), although due to the nature of the study design, direct comparison of Level 2 switching and combining treatment strategies was not available. Overall, Level 1 and 2 treatment results indicate that clinicians can expect close to 50% of all MDD patients to achieve remission by trying two antidepressant treatments (via switching or combining) for adequate duration and dosage.

Patients undergoing Level 3 trials (those failing to achieve remission or experiencing intolerable effects from two antidepressant treatments (Levels 1 and 2)) were randomly assigned to an augmentation or switching strategy (Nierenberg et al. 2006; Fava et al. 2006). Patients in the augmentation trial were randomly assigned to receive citalopram with either lithium (a mood stabilizer) or triiodothyronine (T3; a thyroid hormone which may accelerate

patient response to antidepressants; Aronson et al. 1996). Those in the switch trial were randomly assigned to switch to mirtazapine (atypical antidepressant) or nortriptyline (tricyclic antidepressant). Overall, the augmentation trial showed remission rates at approximately 19-20% with no difference between lithium and T3 augmentation. However, those augmenting with lithium reported greater intolerable effects than with T3 (Nierenberg et al. 2006). Switching for Level 3 treatment showed comparable remission rates between mirtazapine and nortriptyline (overall remission at 10-16%) with similar tolerability across switching treatments (Fava et al. 2006).

Lastly, a Level 4 treatment trial was made available to patients who had failed to achieve depression remission (or experienced intolerable effects) with the three prior antidepressant treatments. In this trial, patients were randomly assigned to switch to either tranylcypromine (monoamine oxidase inhibitor) or given a combination of venlafaxine (serotonin-norepinephrine reuptake inhibitor) and mirtazapine. Both treatments lead to similar remission rates (overall remission roughly 10-15%; McGrath et al. 2006).

Overall, results from the STAR\*D treatment trials generally mirror typical treatment strategies found in clinical practice for nonpsychotic MDD patients in an outpatient setting. Results indicate that roughly half of all MDD patients can expect to achieve symptom remission after two antidepressant treatments, with subsequent switching, combining, and/or augmentation trials leading to diminished remission rates over time. Taking all of the STAR\*D data, Rush et al. 2006 estimated remission rates at Levels 1-4 at 36.8%, 30.6%, 13.7%, and 13.0%. Cumulative remission rates through Level 4 was estimated to be at 67%, indicating that roughly 33% of patients will not have achieved remission by their fourth trial. While there are limitations to the study design (lack of placebo, open-label treatment, lack of variety in Level 1 treatment, etc.), it provides clinicians information about what they might possibly expect from MDD patients over the course of sequential pharmacotherapy trials.

### **Non-Pharmacologic Treatments**

Non-pharmacologic options have shown some promise for treating TRD, although the variety of treatments are less varied than pharmacologic interventions. Some commonly encountered treatments are: psychotherapy, electroconvulsive therapy, vagus nerve stimulation, and repetitive transcranial magnetic stimulation.

Cognitive-behavioral therapy (CBT) and its derivatives have shown to be somewhat effective in combination with antidepressants in individuals showing some antidepressant-resistance. For example, in a group of SSRI-resistant adolescents (similar to the Level 1 resistance found in the STAR\*D trials), a combination of CBT and switching to another antidepressant (either within class or out-of-class) shows greater clinical response than those solely switching to another antidepressant alone (Brent et al. 2008). One of the Level 2 trials in the STAR\*D study also examined switching from citalopram (Level 1 non-remission patients) to cognitive therapy or augmenting citalopram with cognitive therapy. Results from this Level 2 STAR\*D study found that cognitive therapy lead to similar remission rates as Level 2 antidepressants (23-30%), regardless of whether it was used alone or as an add-on to

citalopram treatment (Thase et al. 2007). However, the time to reach comparable remission rates took longer in the cognitive therapy augmentation group (cognitive therapy + citalopram) compared to the citalopram augmentation (citalopram + another antidepressant medication).

Electroconvulsive therapy (ECT) has shown to be quite effective, even showing evidence for being superior to some forms of antidepressants in patient response (Pagnin et al. 2004). However, it is rarely used as a first-line treatment; it is typically used as a last resort for patients. For example, it may be provided as an option for suicidal patients (Kellner et al. 2005) or when pharmacotherapies have been ineffective (Husain et al. 2005). While improvements in mood occur fairly rapidly, relapse is relatively high after ECT (Shelton et al. 2010). While maintenance ECT may prevent some relapse, memory impairments from this treatment can deter patients from opting for this treatment.

Vagus nerve stimulation (VNS) was approved by the FDA in 2005 for use in TRD, and it seems to be relatively well tolerated in patients (Nemeroff et al. 2006). Roughly 25-30% of patients have been shown to respond to VNS, with remission rates around 15-17% over short-term VNS (Nemeroff et al. 2006).

Repetitive transcranial magnetic stimulation (rTMS) is used experimentally to treat TRD and shows some effectiveness in response (Shelton et al. 2010). However, results also vary due to considerable methodological differences suggesting further study.

To conclude, the STAR\*D trials - which mirror the sequential treatment strategies (pharmacotherapy and psychotherapy) typically found in clinical practice – showed that roughly two-thirds of nonpsychotic MDD patients will eventually achieve remission by their fourth treatment trial with adequate time and dosing. This also highlights that, with current strategies for addressing treatment-resistant individuals, there still remains a subset (~ 1/3) whose needs may not be satisfactorily met with current interventions. Besides the challenges of treatment-resistance, relapse is always a concern at any level of treatment, with relapse being more likely to occur for patients requiring more treatment steps. For example, 33% of those who achieved remission at Level 1 will relapse within a year while half of those who achieve remission by Level 4 will relapse within a year (Rush et al. 2006). Relapse also occurs earlier the more treatments steps a patient experiences (Rush et al. 2006).

## **Pre-Clinical Research**

Preclinical research studies have begun in earnest since initial speculations about the role of the endocannabinoid system in depression pathophysiology (Hill & Garzalka 2005). This includes delivering phytocannabinoids (THC and CBD) as well as synthetic cannabinoids in animal models of depression. There has also been interest in manipulating the pharmacokinetic processes of cannabinoids (e.g., metabolism of cannabinoids) with novel compounds to also improve depressive symptomology in animal models. Representative cases of such studies are described below.

**Bambico FR, Hattan PR, Garant J-P, Gobbi G. Effect of delta-9-tetrahydrocannabinol on behavioral despair and on pre- and postsynaptic serotonergic transmission. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2012; 38: 88-96.**

This experimental study explored the administration of THC on serotonergic (5-HT) activity and depressive-like behavior in rats. SSRIs, which are often a first line treatment for depression, increase 5-HT transmission (particularly in the dorsal raphe and hippocampal regions). Therefore, this particular study explored whether THC might have similar effects as SSRIs on 5-HT<sub>1A</sub> activity and induce antidepressant-like behavior in rats. Different rat groups received intraperitoneal injections of either THC (1 mg/kg), citalopram (an SSRI; 10 mg/kg), or vehicle solution (control), which were administered either as a single injection or repeated injections (over 5 days). In some cases, the CB-receptor antagonist rimonabant was also administered to examine for reversal of THC's effects in electrophysiological and behavioral measures.

Electrophysiological recordings were conducted in dorsal raphe and hippocampal 5-HT<sub>1A</sub> neurons. For the behavioral measure, the forced swim test (FST; Porsolt et al. 1977; Can et al. 2012) was implemented to measure for depressive-like behaviors. The FST has often been used on rodents (typically rats and mice) in preclinical trials to test for efficacy of antidepressants. In the FST, rodents are placed into a cylinder filled with water levels sufficient to require them to engage in locomotor activity in order for them to not drown. Within this apparatus they cannot escape, and rodents can adopt a more active or passive coping strategy to survive in this environment. When rodents are actively engaged in not drowning, they will show significant locomotor activity (swimming, attempts to climb the walls of the cylinder, etc.) to stay afloat in the water. A more passive coping strategy typically manifests as significantly reduced locomotor activity that is just sufficient enough to keep them above water—this particular behavior is interpreted as learned behavioral despair (hopelessness or “giving up”). Rodents engage in the FST for two trials, the second of which is the trial of interest where measures of locomotor activity are collected (first trial introduces the rat to the environment and serves as a learning phase). The amount and duration of immobility, climbing, and swimming are recorded as dependent measures during the second FST trial. If rodents in an active treatment group spend less time in passive survival mode compared to control, a drug is interpreted as having antidepressant effects.

Repeated injections of THC (1 mg/kg) as opposed to a single injection of THC increased the frequency of swimming behavior in the FST, comparable to the citalopram rat group (compared to controls). Both the THC and citalopram groups showed decreased total time spent in an immobile state in the FST compared to controls, with the administration of rimonabant with THC reversing this effect. Electrophysiological recordings from the dorsal raphe 5-HT<sub>1A</sub> neurons showed inhibitory, excitatory, and inert responses (neither inhibitory or excitatory) upon intravenous administration of THC (0.1-1.5 mg/kg). With concurrent administration of rimonabant, the excitatory responses that were elicited in some dorsal raphe 5-HT<sub>1A</sub> neurons were blocked, effectively suggesting a role of cannabinoids in facilitating 5-HT transmission. 5-HT<sub>1A</sub> neurons also showed enhancements in tonic receptor activity in the

hippocampus, which mirrors hippocampal 5-HT<sub>1A</sub> tonic receptor activity with traditional antidepressant drugs.

**Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SRL. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT<sub>1A</sub> receptors. *British Journal of Pharmacology*. 2010; 159 122-128.**

This study was a set of three experiments investigating the effects of CBD on depressive-like behavior in rats. It also examined the role CBD might have in activating 5-HT<sub>1A</sub> receptors by the combined delivery of a 5-HT<sub>1A</sub> receptor antagonist and CBD. Lastly, due to some evidence suggesting that hippocampal brain-derived neurotrophic factor (BDNF) expression may increase with antidepressant drugs, the authors looked for a similar increase in BDNF expression with CBD.

- Experiment 1: Performance of CBD-injected rats (3, 10, 30, or 100 mg/kg) compared to imipramine-injected rats (30 mg/kg; a tricyclic antidepressant) and control (vehicle solution) on the forced swim test (FST) and open field test (OFT)
- Experiment 2: FST performance between the following rat groups
  - WAY100635 (a 5-HT<sub>1A</sub> receptor antagonist) + CBD (30 mg/kg)
  - WAY100635 + vehicle solution
- Experiment 3:
  - Performance of CBD-injected rats (30 mg/kg) compared to imipramine-injected rats (30 mg/kg) and control on the FST
  - Analysis of brain-derived neurotrophic factor (BDNF) expression in the hippocampus between groups

The FST (Porsolt et al. 1977) measures a dimension of depressive behavior called learned behavioral despair, while the OFT measures anxiety-like behaviors (please see study directly above for details on the FST). In the OFT (Hall & Ballachey 1932), rodents are placed in a flat, open arena where they can freely roam (walls mark the boundary of this open field from which they cannot escape, and the open field is free of any objects or obstacles). The OFT is used to examine for anxiety-like behavior in rodents particularly to assess anxiolytic properties of drugs. Exploratory duration and behavior are the typical dependent measures in the OFT, although the specific operational definitions for both can vary across studies. In this particular study, researchers measured immobility time in the FST. The dependent measure in the OFT was distance traveled in the open space.

Compared to controls, the CBD (30 mg/kg) and imipramine groups both showed decreases in immobility time on the FST (Expt. 1 and 3), suggesting equivalency of both drugs in treating depressive-like behavior (learned behavioral despair). In addition, injection of a 5-HT<sub>1A</sub> receptor antagonist (WAY100635) reversed the effects of CBD on the FST when compared to a CBD-only group (Expt. 2). No differences were found in the OFT between treatment groups (CBD, imipramine, and control). Lastly, the decreased immobility time that was found in the

CBD and imipramine groups on the FST was not associated with increased expression of BDNF in the hippocampus (Expt. 3). Authors concluded that the efficacy of CBD on depressive behaviors may follow an inverted U-shaped curve where a mid-range CBD dosage (30 mg/kg) may produce antidepressant-like effects equivalent to existing antidepressant treatments. In addition, since serotonergic (5-HT) receptor antagonism reversed CBD's behavioral effects, CBD may influence 5-HT transmission—a neurotransmitter system highly implicated in depressive symptomatology. Finally, contrary to some evidence, the reduction in depressive-like behavior on the FST was not associated with increased BDNF expression for either the CBD or imipramine groups.

**Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proceedings of the National Academy of Sciences*. 2005; 102(51): 18620-18625.**

Researchers in this study administered a fatty acid amide hydrolase (FAAH) inhibitor (slows breakdown of anandamide, an endocannabinoid) and observed for antidepressant-like activity in rats, as well as observing for any changes in 5-HT and noradrenergic (NE) transmission (both neurotransmitter systems implicated in mood regulation). Performance on the forced swim test (FST) and tail suspension test (TST) were observed with single or repeated intraperitoneal injections of URB597 (an FAAH inhibitor), desipramine (a tricyclic antidepressant), or a CB-receptor antagonist rimonabant in conjunction with URB597. (FST has been previously discussed above as a method for measuring of antidepressant-like efficacy in rodents; therefore, FST procedure will not be described here). Similar to the FST, the TST is considered a measure of learned behavioral despair as rodents cope with an inescapable, aversive environment. It is therefore commonly used in assessing antidepressant efficacy in rodents. In the TST, rodents are suspended by their tails causing them to face downward. While rodents initially engage in active locomotor activity (strategies to upright itself), suspension over time generally gives way to passive coping strategies (i.e., greater time spent in an immobile state). In this particular study, immobility time was the primary measure on the TST, while time spent on floating, swimming, and struggling were the primary measures in the FST.

Results from Gobbi et al. showed that higher, single doses of URB597 lead to observable decreases in immobility time when compared to control (vehicle solution), with a 0.1 mg/kg dose of URB597 showing equivalency in immobility time reduction to a single 20 mg/kg and 10 mg/kg dose of desipramine and paroxetine (an SSRI), respectively. In addition, a single dose of rimonabant (1 mg/kg) prior to URB597 administration reversed the immobility time reduction to levels similar to control. Results on the FST with repeated injections of URB597 also showed similar trends (greater reductions in immobility time with higher dosages) and a reversal of effects with rimonabant administration. Lastly administration of URB597 increased 5-HT and NE neuronal firing respectively in the dorsal raphe nucleus and the locus ceruleus, with rimonabant administration reversing this effect.

## Clinical Trials

A search through MEDLINE and ClinicalTrials.gov in mid- August 2016 yielded no published or on-going studies investigating the effects of cannabis or cannabinoids on treatment-resistant depression (or major depressive disorder more generally) as a primary measure. However, a search for endocannabinoid system modulators resulted in one completed study experimenting with a novel FAAH inhibitor on major depressive disorder. This study, while not published in a journal, is listed on the study sponsor's website with details on some methodology and results: [An Eight-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Finding Study, with Escitalopram \(10 mg daily\) as Active Control, to Evaluate the Efficacy, Safety and Tolerability of Three Fixed Doses of SSR411298 \(10, 50, or 200 mg daily\) in Elderly Patients with Major Depressive Disorder \(FIDELIO\)](http://en.sanofi.com/img/content/study/DFI10560_summary.pdf) ([http://en.sanofi.com/img/content/study/DFI10560\\_summary.pdf](http://en.sanofi.com/img/content/study/DFI10560_summary.pdf))

This Sanofi-sponsored trial was a multi-center randomized, double-blind, placebo-controlled study investigating the effects of an endocannabinoid system modulator compared to a selective serotonin reuptake inhibitor (SSRI escitalopram) and placebo on depression symptoms in elderly MDD patients (n = 525). The endocannabinoid system modulator being tested was SSR411298, which is a fatty acid amide hydrolase (FAAH) inhibitor, which effectively slows the metabolism of endocannabinoids. Patients in the study (n = 525) were 60 years or older and had been diagnosed with MDD, as well as having been documented to have had a recurrent episode at least 1 month prior to their first visit for the trial. Patients were given either SSR411298 (at 10 mg (n = 105), 50 mg (n = 106), or 200 mg (n = 105)), Escitalopram (10 mg, n = 103), or placebo (n = 106) via the oral route. Treatment duration was 8 weeks. The primary measure was the 17-item Hamilton Depression Rating Scale (HAM-D). Secondary measures were: 1) Montgomery and Asberg Depression Rating Scale, 2) Clinical Global Impression scale, 3) Hamilton-Depression mood, factor, and core items, 4) 15-item Geriatric Depression Scale, 5) Sheehan Disability Scale, and 6) Hamilton-Anxiety Rating Scale. At Day 56 of treatment, none of the SSR411298-treated groups showed any significant change from baseline on the HAM-D total score compared to placebo. This was in contrast to the escitalopram group which did show significant decrease in the HAM-D score from baseline when compared to placebo. Therefore, while patients in the escitalopram group did show improvements in depression symptoms, those in the SSR411298 group did not show the same effect. Results from secondary measures are sparse, with the only statement suggesting that efficacy from secondary measures cannot be conclusively determined. Some study details were listed on ClinicalTrials.gov, although more information is contained on Sanofi's website (link provided above): [An Eight-Week Study of SSR411298 as Treatment for Major Depressive Disorder in Elderly Patients \(FIDELIO\)](https://clinicaltrials.gov/show/NCT00822744) (<https://clinicaltrials.gov/show/NCT00822744>)

## Observational Studies

No observational studies were found that systematically investigated cannabis use in individuals to specifically treat depression. However, there has been some research to explore whether cannabis use increases depression risk due to some evidence linking mental health

issues with cannabis use. While these cannabis-depression relationship studies are not specifically approached to understand if cannabis can treat depression, any studies that explore this question can be used to evaluate for any evidence of cannabis helping to alleviate depression (if cannabis use isn't associated with increased depression risk, is cannabis use associated with decreased depression risk?). Recent longitudinal studies suggest no risk to slightly elevated risk of depression with cannabis use, with representative cases of these studies discussed below. The final study included in this section is a cross-sectional survey that investigated cannabis use and depression.

**Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. the association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*. 2014; 44: 797-810.**

This meta-analysis examined the association between cannabis use and depression from longitudinal studies. Criteria for meta-analysis inclusion were 1) publication within a peer-reviewed journal, 2) prospective longitudinal, population-based data, 3) exposure variable explicitly defined as cannabis use rather than substance use, 4) depression as the outcome variable (depressive symptoms and/or clinical depression), 5) study controlled for baseline levels of depression in their participants or excluded participants who already had depression at the start of the study, and 6) study presented data with an odds ratio (OR) of depression risk from cannabis use, or presented data in a way that would allow for calculation of OR. This resulted in 14 articles being included in the meta-analysis of a total of n = 76,058 participants.

Main findings: when comparing cannabis use against controls, the pooled OR was 1.17 indicating slightly elevated risk for depression with cannabis use. In a separate analysis of heavy cannabis users (using cannabis at least once a week or having cannabis use disorder), the OR increased to 1.62. When these analyses were recalculated with a subset of studies scoring highest on methodological quality (8 studies), the pooled OR of these studies was 1.12 and 1.34 for cannabis users and heavy cannabis users, respectively. Overall, this meta-analysis indicated a slightly increased risk of depression with cannabis use, with this risk increasing with heavier cannabis use. However, it should also be noted that the lowerbound of the 95% confidence intervals for these ORs were close to 1, which calls for further study and standardization of methods across studies to better understand the relationship between cannabis use and depression.

**Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. *Addiction*. 2006; 101: 1463-1472.**

This study analyzed cannabis use frequency and depression symptoms from participants in the National Longitudinal Survey of Youth of 1979 (NLSY79). While the survey collected data periodically from youths starting in 1979 (including cannabis use patterns), a depression measure was not included until the 1990s using the Center for Epidemiological Studies Depression scale (CES-D; Radloff 1977). Therefore, analysis of the relationship between cannabis use and depression was on longitudinal data at adulthood.

Two main questions were explored in this study that were addressed in two different models: 1) whether depressive symptoms were associated with past-year cannabis use (Model 1), and 2) whether depressive symptoms were associated with the last few years of cannabis use (4 years; Model 2). Essentially, the two models addressed whether depressive symptomology manifests rapidly or slowly with cannabis use. To control for any differences at baseline across participants, the authors used measures collected at the beginning of the survey (or the first time it was collected in the survey) as baseline covariates. This resulted in 55 and 82 baseline covariates being selected for control in Model 1 and Model 2, respectively. In total, 1252 past-year cannabis users and 7498 non past-year cannabis users were included in Model 1. A total of 184 cannabis users (last few years of cannabis use) and 1805 non users were included in Model 2. Authors used propensity score weighting to create comparison groups (users vs. non-users) that would only differ on their cannabis use in consideration of baseline covariates. Overall results on weighted data showed a nonsignificant odds ratio (OR) of 1.13 in Model 1, suggesting no increased risk of depression within one year of cannabis use. Similarly, Model 2 results showed a nonsignificant OR of 1.51. Limitations should also be considered, however, given that both Models still had ORs greater than 1 and that Model 2 was underpowered (which explains the greater spread in the 95% confidence interval in this model). Therefore, if there is any observed risk of depression with cannabis use, careful control of confounding factors may eliminate most or all of this apparent risk. While this study highlights the usefulness of methods in controlling for baseline covariates, it also emphasizes the need for greater systematic, prospective study of variables to avoid such intensive post-hoc variable control to avoid overfitting propensity score models.

**Denson TF, Earleywine M. Decreased depression in marijuana users. *Addictive Behaviors*. 2006; 31(4):738-42.**

This study is included in this section because it is sometimes cited and interpreted erroneously as evidence that cannabis use can decrease depression. This study, which received grant support from the Marijuana Policy Project, was an internet survey which recruited individuals via drug policy organizations (organizations not disclosed in paper). A total of  $n = 4494$  participants completed the internet survey which included items from the Center for Epidemiological Studies Depression scale (CES-D; Radloff 1977) as well as questions on frequency of cannabis use. Whether the survey itself was just restricted to CES-D questions and frequency of cannabis use is not clear, nor are the instructions that were given to participants to specify the purpose of the study. Frequency of cannabis use was used to group participants into three user group categories: 1) Daily Users ( $n = 3323$ ), 2) Weekly Users ( $n = 861$ ), and 3) Never Users ( $n = 310$ ). Total scores on the CES-D were subsequently analyzed and compared across these three participant groups, as well as comparing participant groups by CES-D scale's 4 sub-domains of depressed affect, positive affect, somatic and retarded activity, and interpersonal symptoms. Authors indicated that the Never Users group reported more depressive symptoms than both the Daily Users group and Weekly Users group (the Daily User group and Weekly Users group did not significantly differ in CES-D scores). However, when reviewing the total scores between the 3 participant groups, none of the three groups' scores reached the threshold to indicate clinical depression risk. A score of 16 or higher on the CES-D is typically indicative of some depressive symptomology that may require further clinical

assessment for depression (Radloff 1977). In contrast, total scores in this paper (reported as trimmed means) were several points below this threshold (~5-8 points below threshold), which indicates that all patient groups – regardless of their cannabis usage frequency – were not within the range indicative of clinical depression risk. Therefore, any statistical differences reported between groups in this paper is measuring differences in CES-D scores in individuals that are, overall, not depressed. Lastly, it should be noted that the study did not include any information to decipher whether survey participants also consumed other substances regularly besides cannabis. Since depression is correlated with the use of other substances, it is unclear whether it would have been appropriate for the study to control for this particular confound in their analyses.

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of treatment-resistant depression were found.

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN (zip) 55164-0882  
(phone) 651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Diabetes: Blood Sugar Control

AUGUST 2016

## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Diabetes mellitus is a group of conditions that affect the body's ability to produce or use insulin, a pancreatic hormone circulated through the bloodstream that acts to regulate blood glucose levels. This includes chronic diabetes (type I and type II diabetes) and reversible diabetes (prediabetes and gestational diabetes).

## **Type I Diabetes**

The exact cause of type I diabetes is unknown, but believed to be a combination of genetic and environmental factors. This condition occurs when the immune system attacks and destroys insulin-producing  $\beta$ -cells in the pancreas. As a result, there is very little to no insulin available to regulate blood glucose levels (Mayo Clinic).

## **Type II Diabetes and Prediabetes**

The cause of poor blood glucose control in prediabetes and type II diabetes is insulin resistance that develops over time: cells need increased amounts of insulin to respond and the pancreas cannot produce enough to meet the increased demand. As with type I diabetes, prediabetes and type II diabetes develop due to a combination of genetics and environmental factors; overweight and obesity are contributing, though not necessary, factors. Prediabetes is characterized by a state of impaired glucose control which has not yet advanced to full diabetes, but will likely do so in the absence of intervention. Type II diabetes is a progressive condition which may require ongoing modifications to the treatment plan. (Mayo Clinic)

## **Gestational Diabetes**

Gestational diabetes is caused by insulin resistances in cells caused by the release of hormones during pregnancy which increase insulin resistance.

## **Diagnosis**

Diagnosis of type I and II diabetes and prediabetes involves a blood test for glycated hemoglobin (HbA1c) levels, which reflects the percentage of blood sugar attached to hemoglobin and indicates average blood sugar level over the past two to three months (Mayo Clinic). Normal HbA1c levels are below 5.7%; prediabetes is indicated by HbA1c levels between 5.7% and 6.4%; levels of 6.5% or more indicate diabetes. In addition to measuring HbA1c levels, random or fasting blood sugar tests or an oral glucose tolerance test can be used to diagnose diabetes. Gestational diabetes is diagnosed through an initial glucose challenge test and follow-up glucose tolerance testing.

## **Complications and Consequences**

Serious complications are associated with diabetes, and the risk of such complications rises with poor glycemic control. Acute consequences of poor blood glucose control include hyperglycemia, or high blood sugar, and hypoglycemia, or low blood sugar. Acute hyperglycemia can progress to ketoacidosis, or a diabetic coma. Acute hypoglycemia can progress to seizures, loss of consciousness and a coma. Complications include macrovascular complications such as heart disease, heart attacks or stroke, as well as microvascular complications including neuropathy which can result in severe pain and loss of feeling in affected limbs, nephropathy which can ultimately lead to kidney failure, and retinopathy which can lead to blindness. Another common diabetes complication is foot damage, resulting from neuropathy or poor circulation; this can lead to infections and ultimately amputation (Mayo

Clinic). Finally, diabetes is associated with premature death from all-cause mortality, mortality related to vascular causes, cancer and other causes, with worse outcomes associated with increased blood glucose levels (The Emerging Risk Factors Collaboration 2011).

## Prevalence

The Centers for Disease Control and Prevention (CDC) estimated in a 2014 report that 29.1 million Americans, or 9.3% of the population had diabetes mellitus, of which as estimated 8.1 million were undiagnosed. Type I diabetes cases were estimated at 1.25 million, or 4% of the diabetes burden. Estimates for prevalence of prediabetes are much higher: 86 million Americans over 20 years of age had prediabetes (CDC National Diabetes Statistics Report, 2014).

## Current Therapies

The American Diabetes Association describes a comprehensive evaluation following diagnosis that involves a thorough review of medical history, a physical examination, laboratory evaluation and referrals to specialized medical care. The goals of such an evaluation are to classify the patient, detect any diabetes-related complications that have arisen and develop an individualized care plan for future management of the disease. Treatment for diabetes often involves a holistic approach which includes targeting health behaviors, including a healthy diet and regular physical activity. Glycemic control (management of blood sugar) is a primary measure of diabetes care, as it has been shown to decrease incidence of microvascular complications including retinopathy, nephropathy and neuropathy (Diabetes Control and Complications Trial Group [DCCT/EDIC] 2000). Two major clinical trials, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that maintenance of HbA1c levels at approximately 7% is associated with fewer long-term complications, though treatment regimens that achieved these levels were associated with weight gain and increased risk of hypoglycemia (Lawson 1999). The American Diabetes Association position statement on standards of medical care recommend target ranges of HbA1c and plasma glucose but stress that treatment goals should be individualized and include consideration of balancing the risk of hypoglycemia with benefits from glycemic control.

Prediabetes patients can often successfully manage their blood glucose through lifestyle modification; a randomized clinical trial from the Finnish Diabetes Prevention Group found that lifestyle intervention (counseling on nutrition and weight loss) reduced the risk of developing diabetes in prediabetic subjects by 58% over the 3.2 year average study follow-up (Tuomilehto 2001).

Type I diabetes patients require insulin therapy; type II diabetes patients do not necessarily require pharmacotherapy. Some type II diabetes patients can manage blood glucose levels with diet modifications and exercise alone, however use of oral antidiabetic medications is very common. There are a few classes of oral antidiabetic medications; the most commonly

used is metformin, which decreases the amount of glucose released from the liver. Other oral antidiabetic groups include sulfonylureas, meglitinides and DPP-4 inhibitors, which stimulate insulin release; thiazolidinediones, which increase insulin sensitivity; and alpha-glucosidase inhibitors, which slow the absorption of carbohydrates into the blood stream. Combinations of oral antidiabetic agents are also commonly used to achieve greater glycemic control. It is not uncommon for patients with type II diabetes to progress to the point where insulin is required.

Insulin regimens for diabetes are often characterized as either intensive therapy or conventional therapy. Conventional therapy was defined in the DCCT as typically consisting of multiple daily injections including mixed short-acting and intermediate-acting insulin, along with self-monitoring of urine and blood glucose and adjustments made occasionally based on overall health. Intensive therapy was defined in the trial as involving more frequent injections of both short-acting and long-acting insulin, where the dosage is calculated based on periodic blood glucose tests throughout the day, food intake and anticipated exercise. Intensive therapy has more stringent target ranges for blood glucose levels. There is evidence that intensive therapy regimens reduce the risk of microalbuminuria (Coca 2012), one of the complications associated with poor glycemic control which is associated with poor renal and cardiovascular outcomes (Basi 2008).

The CDC report estimated the prevalence of different diabetic therapies in the U.S. using 2010-2012 data from the National Health Interview Survey: an estimated 2.9 million American adults use insulin only; 3.1 million adults use both insulin and oral antidiabetic agents; 11.9 million use oral antidiabetic medications only and 3 million use neither therapy for the treatment of diabetes (CDC National Diabetes Statistics Report, 2014).

Individual management of blood glucose requires diligent adherence to a prescribed medication regimen often combined with lifestyle modification; as a result, many diabetic patients do not maintain their blood glucose within the recommended ranges. Cross-sectional health data from the U.S. collected from 2005-2010 reports that approximately 41.2% of diagnosed diabetes cases may not maintain HbA1c levels below 7%, based on laboratory testing at the time of survey administration (Selvin 2014).

## **Pre-Clinical Research**

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors to which cannabinoids bind, is still a relatively new field of scientific inquiry. Translational research has shown that endocannabinoids play an important role in lipid and glucose metabolism in peripheral organs (Silvestri 2013) and therefore may be a target in diabetes therapy whose goal is to manage glucose levels. There is a limited number of animal studies examining the effects of cannabinoids on metabolic processes and dysfunction; one aspect of these processes of interest in diabetes treatment is the regulation of glucose tolerance and insulin sensitivity. The following is a sample of animal studies which address the relationship between cannabinoids and regulation of blood glucose levels. The two studies described below represent the level of

evidence currently available in pre-clinical studies to describe the effect of cannabis on measures of diabetes disease burden.

**Levendal R-A, Schumann D, Donath M, Frost CL. Cannabis exposure associated with weight reduction and  $\beta$ -cell protection in an obese rat model. *Phytomedicine* 19(2012) 575-582.**

This study used rat models to examine the effect of cannabis on  $\beta$ -cell secretory function in obese rats. Four groups were observed over a four-week period: an untreated lean control group, a cannabis-treated lean experimental group, an untreated obese control group, and a cannabis-treated obese experimental group. Rats in both experimental groups were injected with 5 mg THC/kg cannabis extract; control groups were injected with an equivalent amount of the vehicle solution. Insulin sensitivity was measured through blood glucose levels after a glucose bolus injection. Post-experiment plasma insulin levels were also examined using a rat insulin radioimmunoassay. Plasma levels of interleukin-1 $\alpha$  and interleukin-1 $\beta$ , interferon- $\gamma$  and tumor necrosis factor- $\alpha$  were also measured. The study found that cannabis exposure significantly increased food consumption in lean experimental rats compared to lean control rats but decreased food intake in obese experimental rats compared to the obese control group, though intake was still higher in this group compared to lean rats. The experimental data was used to generate a predictive polynomial model for body weight; the model showed that body weight increased for all groups, but cannabis exposure was associated with lower weights in both the obese and lean experimental groups compared to the obese and lean control groups, respectively. Analysis of plasma insulin and glucose levels found that while differences were noted between obese rats and lean rats (significantly lower blood glucose levels), no differences were found when comparing experimental rats to control rats in either obese or lean groupings.

No significant differences were found in glucose tolerance when comparing cannabis-exposed rats to unexposed rats in either the lean or obese groupings. In lean rats exposed to cannabis, increases in interleukin-1 $\alpha$  and interleukin-6 compared to lean control rats were observed. In obese control rats compared to lean control rats, lower levels of interleukin-1 $\alpha$ , interleukin-6 and interferon- $\gamma$  were observed. Obese experimental rats had higher levels of interleukin-6 and interferon- $\gamma$  compared to obese control rats.

These findings support the idea that the endocannabinoid system mediates feeding behavior and energy balance and that THC interacts with appetite regulation in a biphasic mechanism- stimulating appetite at low doses and suppressing appetite at high doses. Previous research has found THC retention in fat tissue to be much higher than other tissue; thus high THC levels accumulated in fat tissue could work to suppress appetite. The authors suggest this may account for differences observed between lean and obese rats. However, lean rats were observed to have higher blood glucose levels than obese rats. No differences in plasma insulin levels were observed across groups.

The authors conclude that exposure to cannabis may reduce the negative impact of diet-induced obesity by “reducing weight gain,... maintaining insulin levels, altering cytokine and gene expression levels that induce increased energy expenditure, while protecting

pancreatic tissue from apoptosis,” within a rat model. Protection of  $\beta$ -cell function could be a mechanism of preventing or reducing the severity of diabetes, although this was not directly demonstrated from the scope of this study.

**Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, Gallily R. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. *Autoimmunity*, March 2006; 39(2):143-151.**

This study aimed to examine whether cannabidiol (CBD), a component of the cannabis plant known to have anti-inflammatory properties, could prevent or delay diabetes occurrence in non-obese mice with a high propensity for developing type I diabetes. Cannabidiol was extracted from cannabis resin and injected into female mice with existing insulinitis but without overt disease, who were “chosen to approximate the immunological status of a pre-type 1 diabetic human patient.” Onset of overt diabetes, which was ascertained through urine glucose assays, analysis for insulinitis, and pancreatic histopathology studies of beta cell integrity, occurred approximately at 14 weeks after birth within the study colony; therefore CBD injections were administered to mice up to 12 weeks old. All mice had normal blood glucose levels at the study inception; at ages 6-12 weeks mice in the treatment group were given 10-20 injections of 5mg/kg CBD.

In the control group, 86% of the mice developed overt diabetes at a mean age of 14 weeks; in the treatment group, a reduction in diabetes incidence was observed: 30% of treatment group mice developed overt diabetes ( $p < 0.001$ ). The treatment group mice who developed diabetes had a later onset (median age of 20 weeks,  $p = 0.0001$ ).

While this study may suggest that CBD may play a role in either preventing or delaying the onset of diabetes in patients with prediabetes or who are predisposed to type I diabetes without full onset, it is unclear from the results what role CBD might play in directly modulating insulin resistance or managing blood glucose levels.

## Clinical Trials

Currently there are no clinical trials, either complete or underway, examining the effect of whole plant cannabis, THC, or CBD on blood glucose control. There are, however, the two trials noted below- one completed but unpublished and the other underway- that use tetrahydrocannabivarin (THCV), a cannabinoid typically present in small amounts in cannabis. THCV is a homologue of THC. It has a propyl side chain instead of THC’s pentyl group, which makes it produce different effects than THC.

GW Pharma completed a Phase IIa randomized clinical trial of 62 diabetic patients, where two treatment arms were given oral THCV for the treatment of type II diabetes for a 13-week period. The study results are not published, but the GW Pharma website states the findings were that the oral cannabinoid reduced fasting plasma glucose levels, increased fasting insulin levels, improved pancreatic  $\beta$ -cell functioning; additionally it had other antidiabetic effects including increasing serum adiponectin, reducing systolic blood pressure and serum interleukin-6 levels. Non-significant findings include increased insulin sensitivity,

reduced HbA1c levels, improvement in glucose and insulin response to glucose load, increased glucagon-like peptide-1 levels and reduced C-reactive protein levels. More information about this trial can be found [GW Pharma's Research and Development](http://www.gwpharm.com/Diabetes.aspx): <http://www.gwpharm.com/Diabetes.aspx>.

A follow-up trial of the same oral THCv product as an adjunct therapy with metformin in the treatment of type II diabetes is currently enrolling in Romania and the United Kingdom. The trial will last approximately 12 weeks and primary outcome measure will be changes from baseline to trial completion in mean HbA1c level. The principal investigator is Melanie Davies from the Leicester Diabetes Center in Leicester, UK. The projected completion was July 2016; more information can be found at [A Study of GWP42004 as Add on to Metformin in the Treatment of Participants With Type 2 Diabetes](https://clinicaltrials.gov/ct2/show/study/NCT02053272): <https://clinicaltrials.gov/ct2/show/study/NCT02053272>.

## Observational Studies

There are a number of relatively recent epidemiologic studies examining cross-sectional survey data which report mixed findings on the relationship between marijuana use and either the incidence of diabetes or markers of glycemic control (such as insulin and insulin sensitivity, and HbA1c levels). The following summaries are not a complete collection of studies on this topic, but they represent the wide range of results and the complexities of interpreting cross-sectional data. While there are serious limitations in interpreting any reported associations, the strength of these studies is the large and representative population sample they include.

**Penner EA, Buettner H, Mittleman MA. The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults. *The American Journal of Medicine*. 2013 July; 126(7):583-589.**

This paper analyzes data from the National Health and Nutrition Examination Survey (NHANES) from 2005-2010 to characterize the relationship between marijuana use and metabolic processes through the clinical metrics of fasting insulin, glucose and insulin resistance. The study cohort, from a nationally-drawn probability sample, included 4,567 adults and captured both self-reported survey responses and fasting blood samples tested for fasting insulin, blood glucose and homeostasis model assessment of insulin resistance (HOMA-IR) which provides an estimate of insulin resistance. To ascertain marijuana use, subjects were asked if they have ever smoked marijuana or hashish, how long since they last used marijuana/hashish and how many days in the past 30 days they used marijuana/hashish. Responses were categorized as past users (no marijuana use in the past 30 days), current users (use within the past 30 days) and never users, the largest group (n=2103).

Since the study data spanned several years of survey administration, there was variation in the data collected. Some survey cycles included HDL cholesterol testing; others included HbA1c measurements. Other clinical measurements included blood pressure, body mass index (BMI) and waist circumference.

In the study population there were 579 current marijuana users and 1975 past users. After weighting to adjust for the NHANES sampling design and adjustment for potential confounders (age, sex, race/ethnicity, education level, income, marital status, tobacco use, physical activity level, and alcohol use), both past and current marijuana use was associated with 16% lower fasting insulin levels and 17% lower HOMA-IR when compared to the never users; past and current users also had significantly lower BMI. Additionally, current marijuana use appeared to be significantly protective against low HDL cholesterol and high waist circumference. Other metabolic indicators examined were triglyceride levels and systolic and diastolic blood pressure but no significant associations were found between marijuana use and these outcomes. The authors state that the results of their analyses were not different when they eliminated subjects who were known to have diabetes.

Limitations of this study include the cross-sectional study design which makes any interpretation of associations more difficult than randomized clinical trials or studies with retrospective or prospective follow-up. The authors point out that improved metabolic indicators may be the result of a diabetes diagnosis, in which a subject may modify their lifestyle with the intent to improve their health as a response to receiving a new diagnosis. There is also a possibility that other confounders which were not measured as part of this study are in fact mediating the relationship between insulin resistance and marijuana use.

**Rajavashisth TB, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, Friedman Tc. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open*. 2012 Feb 24.**

This study examined the relationship between diabetes occurrence and marijuana usage in data from the National Health and Nutrition Examination Survey III, a cross-sectional study which used a sample generated from highly stratified probability sampling across the US with oversampling for minority groups and older subjects. Marijuana use was classified as non-users which included both never users and subjects who had not used marijuana within the past month. Current users were categorized as either light users ( $\leq 4$  days per month) or heavy users ( $\geq 5$  days per month). Marijuana products included hash, pot, grass, or other references to the cannabis plant; both smoking and ingestion were included.

Diabetes was identified by asking subjects whether they were told they have diabetes or high blood sugar, or with fasting blood glucose levels over 125mg/dl. Of the 8,127 subjects aged 20-59 with complete laboratory data, 719 were identified to have diabetes.

Among all subjects aged 20-59 years regardless of missing laboratory data (n=10,896), 6,667 (62%) were non-users, 3,346 (31%) were past users, 557 (5%) were light current users and 326 (3%) were heavy current users. After adjustment for possible confounders (age, gender, race/ethnicity, BMI, education level, tobacco and alcohol use, physical activity, cholesterol – serum total, HDL and LDL- triglycerides, vitamin D, C-reactive protein, ferritin, fibrinogen, white blood cell count, and uric acid) both past and current marijuana users had lower prevalence of diabetes, although there were no differences in prevalence of hypertension, stroke, myocardial infarction, or heart failure compared to non-users. Of all

usage groups, current light marijuana users had the lowest prevalence of diabetes; current heavy users and past users also had lower prevalence of diabetes compared to never users. The authors postulate that this effect may be due to anti-inflammatory properties of cannabis.

The authors point out that the major limitation of this study is that it examines purely cross-sectional, self-reported data. Though potential confounders were examined carefully, no causal relationships can be determined due to the lack of retrospective or prospective study. Furthermore, the survey only captured information on recreational use without any examination of quantity, formulation or mode of usage (smoked versus ingested). It is therefore difficult to generalize any associations found in this study to cannabis usage through medical cannabis programs.

**Thompson Ca, Hay JW. Estimating the association between metabolic risk factors and marijuana use in U.S. adults using data from the continuous National Health and Nutrition Examination Survey. *Annals of Epidemiology* 25(2015) 486-491.**

The authors of this paper examine the conclusions from a number of other studies based on National Health and Nutrition Examination Survey (NHANES) and similar large-scale datasets. The study reviews NHANES survey data from 2005-2012 to estimate the effect of marijuana use on markers of metabolic disease, including insulin resistance and fasting insulin. Citing that reports have produced mixed conclusions on whether marijuana use is associated with lower risk of metabolic syndrome, the authors used outcome variables of fasting insulin, fasting glucose, insulin resistance, HDL cholesterol, triglycerides, blood pressure, BMI and waist circumference and adjusted for known risk factors of metabolic syndrome: age, sex, race, BMI, tobacco use, physical activity, income, alcohol consumption, carbohydrate intake and postmenopausal status, along with educational level, including imputed values for missing data and including a squared term for age to account for a non-linear relationship between age and any outcomes. As a final check for robustness, alcohol use was substituted for marijuana use in each multivariate model.

The study found that in models adjusted for known risk factors and demographics, fasting insulin, insulin resistance, BMI and waist circumference were all lower in current marijuana users than in never users. The analyses were then stratified by age and sex to account for any effect modification between the predictors; this had a diminishing effect on the associations. All significant effects of marijuana disappeared for subjects 40 years or older, and in subjects under 40, marijuana use remained a predictor of only insulin, insulin resistance and waist circumference. Stratification by sex showed no association between marijuana use and outcomes in women; in men, marijuana use was associated only with reduced HDL cholesterol, BMI and waist circumference. Associations with insulin and insulin resistance dropped out. Finally, replacing marijuana use with alcohol use showed a similar pattern of association: alcohol consumption was associated with higher HDL cholesterol, lower fasting insulin, lower insulin resistance, BMI and waist circumference. The authors conclude that their analyses suggest that previous examinations into the relationship between marijuana use and metabolic risk factors have not been rigorous and therefore the conclusion that marijuana use may lower risk of metabolic diseases, including diabetes, is suspect.

**Alshaarawy O, Anthony JC. Cannabis Smoking and Diabetes Mellitus: Results from Meta-Analysis with Eight Independent Replication Samples. *Epidemiology*. 2015 July; 26(4):597-600.**

This meta-analysis examines the role of cannabis smoking with type 2 diabetes using epidemiologic estimates from eight independent replications from the NHANES data and the National Surveys on Drug Use and Health (NSDUH) from 2005-2012. The authors note that some preclinical studies have found that activation of cannabinoid receptors is linked with increased appetite and insulin resistance, but a number of epidemiologic studies find an inverse relationship between cannabis use and prevalence of diabetes- specifically, prevalence of obesity and biomarkers associated with impaired glucose metabolism.

Both NHANES and NSDUH use probability sampling to generate a sample representative of U.S. residents. Both studies deploy surveys using audio computer-assistant self-interview assessment protocols; NHANES supplements self-reported data with clinical and lab assessments. Diabetes is measured by NSDUH through self-reported questions; NHANES includes self-report but also collects insulin or antidiabetic medication use and lab values to generate a composite diabetes indicator. Cannabis smoking is captured as the following: recently active cannabis smokers, past cannabis smokers, and never smokers. Multiple logistic regressions were performed to produce adjusted odds ratios of diabetes across cannabis use categories; as a follow-up to this analysis, time to onset of diabetes as a function of cannabis use was modeled, as well as time to onset of cannabis use as a function of diabetes incidence to examine the direction of potential causality. The meta-analytic odds ratio, adjusted for age, sex, ethnicity, education, income-poverty ratio, alcohol and tobacco use, for diabetes among recently-active cannabis users (using never users as the reference group) was 0.7 (95% confidence interval: 0.6, 0.9). Additional onset-age analyses as described above were limited by sample size but suggested that cannabis use preceded diabetes onset and reinforced the inverse relationship between cannabis use and diabetes, though not robustly.

Limitations of this study include the cross-sectional nature of the source data and self-reported diagnosis data. Furthermore, the direction of causality remains to be proven as there may yet be confounders which were not measured or adjusted for in this analysis. Nevertheless, the authors conclude that these data show a possible protective effect of cannabis use on the incidence of diabetes.

## **National Medical Organization Recommendations**

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of blood glucose were found.

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Ehlers-Danlos Syndrome

SEPTEMBER 2016

## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Ehlers-Danlos Syndrome (EDS) is a group of inherited connective tissue disorders. They are conditions distinct in clinical features and, where known, genetic basis. Genetic alterations in production of collagen and other components of the extra-cellular matrix as well as in cellular signaling contribute to the clinical features of EDS. Advances in genetic research have rendered the standard classification of EDS, the 1997 Villefranche classification, in need of revision, but it is still in widespread use. The Villefranche classification delineates six types of EDS. Of the six, the following three are by far the most common (Sobey 2014):

## Classical EDS

Joint hypermobility, marked skin hyperextensibility, and widened atrophic scars are its hallmarks. There are also a number of typical skin findings. As with all types of EDS, pain in joints and elsewhere in the musculoskeletal system can be severe. Mutations in type V collagen cause classical EDS. It is dominantly inherited, though severity can vary within the same family.

## Hypermobile EDS

Generalized joint hypermobility with recurring joint dislocations and hyperextensible skin are the characteristic manifestations. Severe chronic joint pain coupled with symptoms of autonomic dysfunction (example – heart rate changes that can lead to fainting when moving to a standing position) can severely impair quality of life and limit opportunities for education and employment. Muscle cramps, headaches, and fatigue are frequently present (Rombaut 2010). The genetic basis of Hypermobile EDS is unknown. The higher prevalence among women remains unexplained.

## Vascular EDS

Structural anomalies in blood vessels – including large blood vessels such as the aorta – make rupture of vessels and of hollow organs (colon, for example) a particular risk for this type of EDS. The skin, rather than being hyperextensible, is thin, translucent, and prone to easy bruising. Joint hypermobility is usually limited to small joints in the hands. Vascular EDS is caused by a gene that codes for type III collagen.

Musculoskeletal pain is a prominent symptom of patients with EDS but the pathophysiology of the pain – the chain of causes that leads to the pain – is not well defined. There are likely multiple causes, including biomechanical/physical determinants, deconditioning, and neurological mechanisms (Scheper 2015). Generalized joint instability may cause the occurrence of micro-traumas on joint surfaces, leading to adaptation and compensation of movement patterns, causing areas of overload on other joints and muscles. Soft tissue laxity could contribute to overload of tendons. Pain could lead to decreased activity resulting in weakness of muscles and loss of proprioception information (position of joints and limbs) causing changes in movement patterns. Research presents some evidence of brain and spinal cord changes leading to increased sensitivity to pain.

Some of the substantial disability in EDs patients might be due to pain-related fear. Fear of pain might trigger avoidance of painful muscle contractions, leading to submaximal muscle performance, resulting in reduction of the force needed to stabilize hypermobile joints. This could lead to a downward spiral of impaired balance, loss of confidence, and further fear of movement and pain (Scheper 2015).

## Prevalence

A widely stated estimate of prevalence of Ehlers-Danlos syndrome is 1 in 5,000 persons. This comes from a book chapter on EDS that cites a wide range of estimates of EDS and gives the 1 in 5,000 as the authors' best guess (Steinmann 2002).

## Current Therapies

No curative therapy is available for EDS, so treatment focuses on relieving symptoms and preventing serious complications. EDS affects multiple body systems and typically EDS patients benefit from a coordinated, multi-disciplinary approach to care. Key aspects of care include physical therapy and occupational therapy, pain management, cardiovascular assessment, and psychological care (Rombauid 2010). Though pain management is well recognized as important for managing patients with EDS, published articles found did not go into detail about specific clinical approaches for EDS – other than to discuss the familiar, untoward side effects that accompany use of opioid drugs.

## Pre-Clinical Research

The pathogenesis of musculoskeletal pain in EDS patients is currently not well-defined. Accordingly, it is not clear what aspects of endocannabinoid system investigations are most relevant for musculoskeletal pain in EDS patients. No published articles were found that focused specifically on animal models of EDS.

## Clinical Trials

No clinical trials were found in the published literature or on ClinicalTrials.gov for studies of cannabis or cannabinoids as therapy for pain or other symptoms in patients with EDS. For purposes of pain management and muscle spasm reduction, published clinical trials in these areas might be applicable. The degree to which each study is relevant to patients with EDS isn't clear however, given the unknowns about the pathogenesis of musculoskeletal pain in this population. Summaries of clinical trials of cannabis and cannabinoids for pain and for severe, persistent muscle spasm can be found in a document maintained by the Office of Medical Cannabis: [\*A Review of Medical Cannabis Studies Relating to Chemical Compositions and Dosages for Qualifying Medical Conditions.\*](#)

<http://www.health.state.mn.us/topics/cannabis/practitioners/compdosagerpt.pdf>

## Observational Studies

No published observational studies were found related to use of cannabis or cannabinoids as therapy for pain or other symptoms in patients with EDS. There are however,

many testimonials and accounts of benefits from use of cannabis in EDS patients on web sites maintained by individuals and by organizations.

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the treatment of Ehlers-Danlos Syndrome were found.

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Insomnia

AUGUST 2016

## Introduction

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Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Insomnia is a persistent condition in which a person has difficulty falling asleep, staying asleep, or both, in spite of the opportunity for adequate sleep (Mayo Clinic). In some cases, insomnia is an independent disorder; however insomnia can often result from another coexisting condition and can also persist even with successful management of the coexisting condition (Bonnet). The Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition (DSM-V) describes major diagnostic criteria for insomnia (American Psychiatric Association 2013):

- Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening
- The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
- The sleep difficulty occurs at least 3 nights per week, is present for at least 3 months, and despite adequate opportunity for sleep
- The insomnia does not co-occur with another sleep disorder
- The insomnia is not explained by coexisting mental disorders or medical conditions

While the DSM-V requires persistence of symptoms for 3 months to constitute a diagnosis, many clinicians consider symptom persistence for one month or longer to constitute chronic insomnia. Additionally, the DSM-V criteria excludes insomnia related to other medical or mental conditions, but many epidemiologic studies include all patients with a defined set of insomnia symptoms, regardless of underlying cause.

According to the Mayo Clinic, symptoms of insomnia may include not feeling well rested after sleep, tiredness, irritability, depression, anxiety, attention deficits as a result during waking hours, as well as tension headaches and gastrointestinal distress (Mayo Clinic).

Insomnia can result from a variety of causes, including stress, anxiety, depression, comorbid conditions including cancer, chronic pain, arthritis, conditions causing respiratory difficulties including heart failure and lung disease, and many others, poor sleep hygiene, environment or schedule changes, medications, intake of caffeine, nicotine or alcohol, eating patterns, and aging (Mayo Clinic).

## **Diagnosis**

Diagnosis of insomnia will require physical examination and interview by a health care practitioner to determine the patient's medical history, to ascertain potential causes of insomnia, and sleep history, to understand the scope of the sleep disturbance and identify potential causes. Health care providers will also perform a physical examination and blood testing to rule out possible causes of sleep disturbance, and in some cases a sleep study, involving overnight polysomnogram (PSG) recording of brain activity, eye movements, heart rate, and blood pressure, to identify or rule out possible underlying sleep disorders.

## **Complications and Consequences**

Serious complications can arise from chronic insomnia. Among patients with chronic illness (a common cause of insomnia), those who also suffered from insomnia reported a lower quality of life compared to chronic illness patients without insomnia (Katz 2002). Ongoing complications related to insomnia include reduced job or academic performance, reduced reaction time, increased psychiatric problems (depression, anxiety), weight gain, irritability, and increased risk of substance abuse and chronic illness related to short-term symptoms including hypertension, heart disease or diabetes (Mayo Clinic).

## Prevalence

Estimating prevalence of insomnia in the general population is challenging because of the variations in defining this condition- some estimates use a broad definition without criteria relating to severity or duration. A clinical review from the Stanford School of Medicine Sleep Disorders Center provides some recent estimates for the various criteria used in the literature. A number of studies estimate the prevalence of insomnia symptoms which occur at least 3 nights a week, “often” or “always” (no duration specified) to be from 16%-21% in the general population (Ohayon 2002). Few studies estimate the prevalence of insomnia diagnoses but a review by Ohayon et al reported that population estimates of the prevalence of insomnia diagnoses including those related to other medical conditions or mental disorders, ranged from 4.4% to 6.4% (Ohayon 2002).

## Current Therapies

Patients suffering from insomnia should receive treatment for any underlying or exacerbating conditions including chronic illness, psychiatric problems, substance abuse or other sleep disorder. A generalized approach includes counseling on sleep hygiene and stimulus control (minimizing other uses of bed or sleeping area such as reading, watching television, etc.) If insomnia symptoms persist in spite of treatment of any underlying conditions, or in the case of isolated insomnia not attributable to any other condition, a patient may receive behavioral therapies beyond basic counseling, medications to treat insomnia, or a combination of behavioral therapy and medication. Bonnet et al compiled a thorough review of current therapies for insomnia and their efficacy and adverse effects in “Treatment of insomnia,” published on Uptodate.com (Bonnet). The following is a summary of Bonnet’s review.

### Behavioral Therapy

A number of behavioral therapy strategies have been found to be effective in treating insomnia. Relaxation therapy is a common strategy that is implemented before each sleep period; two approaches of relaxation therapy are a progressive relaxing of muscles throughout the body until the entire body is relaxed, and a relaxation response approach involving developing a relaxed abdominal breathing rhythm while maintaining a restful position. A few small randomized studies have reported relaxation therapy to be associated with modest benefits in sleep quality when compared to placebo, but not necessarily associated with improved daytime functioning (Means 2000, Edinger 2001). Another common behavioral therapy is sleep restriction therapy, which limits the amount of time the patient spends in bed to counteract the negative effects produced by insomnia patients’ frequent tendency to stay in bed longer and delay sleep onset for the following night. The regimen begins with the patient spending as much time in bed as they report sleeping; this amount is only increased in increments of 15-30 minutes when sleep efficiency (time asleep divided by time in bed) is greater than 85% (Bonnet). A review of four randomized trials of sleep restriction therapy found that sleep restriction therapy was associated with improvements in subjective sleep

variables with an effect comparable to cognitive behavioral therapy (Miller 2014, Montgomery 2003).

Cognitive behavioral therapy (CBT) refers to a therapist-guided short term course consisting of a combination of the behavioral treatments described above, often administered over 6-8 weeks. This may include several therapy sessions, each focusing on a particular behavioral strategy for insomnia treatment. There is a base of strong evidence supporting CBT as an effective therapy; a 2015 meta-analysis combining results from 20 trials, CBT was found to significantly improve sleep onset latency, decrease wake time after sleep onset and improve sleep efficiency when compared with no intervention (Trauer 2015).

While CBT has been shown to be effective for treating some cases of insomnia, one important drawback is the reliance of the therapy on a highly trained clinician; there is evidence that outcomes depend on the amount of experience held by the administering clinician (Espie 2007). Another drawback is the need for a high degree of patient compliance, which is difficult especially in challenging therapies such as sleep restriction.

### **Medication Therapy**

There are several options for pharmacotherapy. Choosing medication requires balancing the potential therapeutic benefit against risks including respiratory suppression, mental incapacitation (decision-making) and addiction. Common medications for insomnia are benzodiazepines, nonbenzodiazepines (drugs molecularly dissimilar from benzodiazepines but producing similar benefits and side effects), melatonin agonists, orexin receptor antagonists, and occasionally other sedatives including antidepressants, diphenhydramine, antipsychotics, and barbiturates. There are few studies directly comparing various medications' efficacy of treating sleep disorders. Selection of a medication, therefore, is often made on the basis of the type of symptoms experienced by the patient. For patients who have difficulty falling asleep, short-acting medications (such as zolpidem or lorazepam) are preferred whereas patients who have trouble maintaining sleep are often prescribed longer-acting medications (such as extended-release zolpidem or eszopiclone).

Adverse effects of insomnia medications can be serious. Benzodiazepines and nonbenzodiazepines can cause residual sedation, drowsiness, dizziness, cognitive impairment, and dependence; they are also respiratory suppressants (Bonnet). Nonbenzodiazepines tend to have less severe adverse effects, as they have shorter half-lives. Melatonin agonists and orexin antagonists are associated with risks including somnolence and headache; melatonin agonists also are associated with risk of dizziness, nausea and fatigue but do not carry great risk of abuse.

Older adults are generally more susceptible to adverse effects of hypnotic medications (including benzodiazepines, nonbenzodiazepines, melatonin, and other insomnia medications); use of these drugs in elderly patients is also associated with increased risk of falls (Gray 2006, Cummings 2003, Kudoh 2004, Tom 2016). Finally, there is observational data showing an increased risk of all-cause mortality and/or cancer with the use of hypnotic medications (Kripke 2012, Hausken 2007, Belleville 2010, Kripke 1998, Weich 2014).

## Pre-Clinical Research

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors to which cannabinoids bind, is still a relatively new field of scientific inquiry. Translational research has shown that the endocannabinoid system may play a role in sleep: Murillo-Rodriguez et al found that anandamide, an endocannabinoid, increases slow wave sleep in rats (Murillo-Rodriguez 2006); Herrera-Solis et al found that anandamide administration in rats increases rapid eye movement (REM) sleep (Herrera-Solis 2010).

## Clinical Trials

A study sponsored by the University Health Network in Toronto (principal investigator: Colin Shapiro) is registered on the NIH Clinical Trials website to study the effect of nabilone, a cannabinoid approved for use in Canada, on sleep disturbance and insomnia in patients with pain. This is a double-blind crossover design that will enroll patients 18-65 years old and use change in sleep efficiency, verified by PSG, as the primary endpoint. The status of recruitment is unclear, as the study details were most recently verified in 2005. [Use of the Cannabinoid Nabilone for the Promotion of Sleep in Chronic, Non-Malignant Pain Patients.](https://clinicaltrials.gov/ct2/show/NCT00384410?term=cannabis+insomnia&rank=3)  
<https://clinicaltrials.gov/ct2/show/NCT00384410?term=cannabis+insomnia&rank=3>

**Ware MA, Fitzcharles M, Joseph L, Shir Y. The Effects of Nabilone on Sleep in Fibromyalgia: Results of a Randomized Controlled Trial. *Pain Medicine*. 2010 Feb; 100(2):604-310.**

This is a randomized, double-blind, active-control trial to assess non-inferiority of nabilone, a synthetic cannabinoid, compared to amitriptyline, a tricyclic antidepressant, in improving sleep quality in fibromyalgia patients. The authors note that prevalence estimates of insomnia in fibromyalgia patients exceed 75%. Each drug was administered for a two-week period, with a two-week washout period between the two phases. Patients were recruited from a pain clinic and were adults with self-reported chronic insomnia (defined as disturbed sleep every other night or every night over the past 6 months). Subjects received either 0.5 mg nabilone or 10 mg amitriptyline at the start of each phase; after 7 days, their dosage either was maintained or doubled, depending on evaluation by a physician. The primary study outcome was sleep quality, assessed with two validated subjective tools: the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ). This study included 29 patients who were randomized and completed the study; in this group, nabilone was found to have a greater positive impact on sleep quality than amitriptyline based on ISI scores. The LSEQ scores comparison showed no difference between the two drugs, though subjects reported more restful sleep while taking nabilone. No other differences were noted in secondary outcomes of pain, mood, or quality of life. Dose adjustment (doubling the dose after 7 days) occurred more frequently when patients took amitriptyline compared to when taking nabilone. While no serious adverse events (AE) occurred during the trial, 91 AEs (most commonly dizziness, nausea, dry mouth and drowsiness) were attributed to nabilone while only 53 were attributed to amitriptyline. The main limitation of this study is the short duration of treatment for each drug;

long-term safety and efficacy remain unknown. Furthermore, any effects of nabilone or other cannabinoids on sleep architecture, versus subjective assessment as is measured in this study, remain unknown.

**Russo EB, Guy GW, Robson PJ. Cannabis, Pain and Sleep: Lessons from Therapeutic Clinical Trials of *Sativex*<sup>®</sup>, a Cannabis-Based Medicine. *Chemistry & Biodiversity*. 2007; 4:1729-1743.**

This 2007 review from GW Pharma, the producer of the cannabis-based medicine Sativex, summarized the results of 13 trials of cannabis-based medicine (6 pain studies; 3 multiple sclerosis studies; 4 other condition studies) with sleep as a secondary outcome. The authors interpret the study results by stating that while there may be no objective sleep effect observed in these trials, there is a consistent subjective benefit perceived by patients with neuropathic pain as well as multiple sclerosis. The review by Gates et al (2014) in the “Observational Studies” section summarizes a number of these studies and their findings, though the most obvious limitation is that they did not examine sleep as a primary outcome in a population with inclusion criteria of sleep disturbances or disorders. These studies are useful in projecting how cannabis therapy may affect sleep disorders within selected populations (multiple sclerosis patients, chronic pain patients, etc.) but they do not address whether cannabis has a therapeutic benefit in patients with insomnia in the absence of an underlying condition precipitating the insomnia.

## Observational Studies

Data on the impact of cannabis on sleep in humans is limited. As with the process of diagnosing insomnia, interpreting the literature surrounding cannabis and its impact on sleep is a challenge because of different measures of impact. Many studies report results from patient self-reported impact of cannabis on sleep quality, which is inherently subjective. However, a smaller number of studies report impacts on objectively-defined measures of sleep, including length of sleep phases and time to sleep onset; these measures can be assessed through a polysomnogram (PSG). A number of these are described in this section.

**Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. *Sleep Medicine Reviews*. 2014; 18:447-487.**

The authors completed a comprehensive review of clinical and observational studies of both medical and recreational cannabis use and its effects on sleep. The authors note that while many recreational cannabis users report sleep as a major motive in cannabis use, there is little data to support or refute its usefulness in treating sleep disorders, specifically insomnia. Limited data that exists is difficult to interpret due to methodological variation (objective versus subjective measures of sleep, lack of control for confounding variables) and small sample sizes. The authors reviewed all findings through the end of 2012; articles describing the prevalence of sleep problems among cannabis users or described the effects of cannabis withdrawal on sleep were excluded. Each paper was assessed for quality and scored accordingly.

Eleven studies were identified which examined recreational cannabis use and its impact on sleep. The authors note that the quality of these studies was poor and subject to a high risk of bias as they did not account for known confounders including age or gender. Of these, six examined objective measures of sleep and five examined subjective measures of sleep. The six studies using objective sleep outcomes yielded inconsistent results- three studies reported a decrease in slow wave sleep while one study reported an increase. One study reported an increase, and another a decrease, in REM sleep while the remaining four found no effect attributed to cannabis use. Of four studies measuring sleep onset latency, one reported an increase in sleep latency and one reported a decrease on a high THC dose. Of the remaining five studies using subjective sleep outcomes, three reported a decrease in sleep latency, but none of the studies reported an effect on night time sleep awakenings. Effects on overall sleep time varied as well. Among recreational use studies, three studied different dosages and found no dose-dependent effects on sleep.

The authors reported on 28 studies on medicinal cannabis as a treatment for other conditions beside insomnia which include measures of sleep-related outcomes; this includes 12 studies with pain patients, 9 studies with multiple sclerosis patients, as well as patients with anorexia, cancer and immune deficiency (7 studies). Included in this group were 14 papers studying synthetic cannabinoids (Marinol, dronabinol or nabilone). The authors rated the quality of this evidence as poor, often due to the use of non-validated sleep measures and lack of adequate blinding to cannabis dose. Of the total 28 studies on medicinal cannabis, 20 report some type of positive impact on sleep. Of the 20 reporting sleep improvements, two reported that improvements dropped off by the end of the experiment and one reported a lessening of bad dreams rather than improved sleep quality or quantity. Five studies compared medicinal cannabis to other medications for sleep outcomes; each compared a different medication. These reports found cannabis to be more effective than diazepam (for patients with anorexia) and amitriptyline (for patients with fibromyalgia and resulting insomnia), and less effective than ketoprofen (among pain and nausea patients), gabapentin (treating neuropathy) and dihydrocodeine (treating neuropathy).

Seven of 28 medicinal cannabis studies reported on validated but subjective measures of sleep (Medical Outcomes Study sleep scale and LSEQ were the most common tools). Here, the results are also varied: four studies which report on sleep disturbance found a reduction in sleep problems; of three studies looking at sleep quality, two found improvements while the third found no effect. Only two studies reported on sleep onset latency, of which one found an improvement (reduction in sleep onset time). Two studies reported on an overall sleep score and one found improvements in sleep while the other found no change associated with cannabis use. Finally, two papers studied night time awakenings and neither found any association in either direction. Of three studies examining dosing effects, two found that higher doses of THC improved sleep more than lower doses.

The authors conclude that current evidence regarding the effect of cannabis or its synthetic analogs on sleep is of poor quality and mixed findings, but they note that among populations with conditions which cause sleep disturbance, cannabis appears to improve sleep quality though not affecting total sleep time. They propose a plausible interpretation of their

findings to be that cannabis may be effective in improving sleep quality among patients with sleep-interrupting symptoms, but may not be beneficial for populations without sleep-disrupting medical conditions. The authors state that the effects of cannabis on various aspects of sleep are yet unclear and due to the risk of bias in the reviewed studies, more longitudinal and well-controlled studies are needed to fully understand these effects.

**Schierenbeck T, Riemann D, Berger M, Hornyak M. Clinical Review. Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana. *Sleep Medicine Reviews*. 2008; 12:381-389.**

This review included 16 PSG-validated studies with small sample sizes (between 1 and 32); six included chronic marijuana users. The authors point out that many limitations to interpreting their results- the studies are small and heterogeneous in subject selection (cannabis-naïve subjects versus habitual cannabis users) and type of cannabis product administered (varying doses, routes of administration and ratios of THC: CBD); additionally, the studies which compare cannabis use to a baseline of no cannabis use within current cannabis users did not account for any cannabis withdrawal effects that could confound results. The authors found that the few reports on cannabis effects on sleep produced conflicting conclusions- in some cases THC was found to decrease the time needed to fall asleep (sleep onset latency) whereas in a few studies, including those using higher doses of THC or marijuana-naïve subjects, sleep onset latency increased. In two studies, slow wave sleep was reduced by cannabis use but there was also a report of increased slow wave sleep. In a few studies, cannabis use was associated with increased sleepiness the next morning. The authors of this review state that the most consistent finding across these studies is that cannabis use decreases total REM sleep and REM density.

**Webb CW, Webb SM. Therapeutic Benefits of Cannabis: A Patient Survey. *Hawai'i Journal of Medicine & Public Health*. 2014 Apr; 73(4): 109-111.**

This article describes the results of a survey distributed to 100 patients re-enrolling in the Hawaii medical cannabis program which asked patients to describe any pain symptoms they experienced before and after medical cannabis treatment (using a universal pain scale), as well as to report any benefits and/or adverse effects. The response rate was 94%; average age was 49.3 years and 97% of respondents reported using cannabis primarily for the treatment of chronic pain. Patients responded to the open-ended question about benefit by reporting relief from stress or anxiety (50%), insomnia (45%) and also reported improved appetite (12%), decreased nausea (10%), increased concentration (9%) and relief from depression (7%). This study has major limitations, in that it relies entirely on self-reported information without any adjudication of diagnosis, symptoms, or relief perceived from cannabis treatment, as well as the selection bias inherent in querying patients who have elected to continue in the medical cannabis program. However, it reflects the consistent impression of patients receiving cannabis treatment that their sleep is improved.

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the treatment of insomnia were found.

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Phantom Limb Pain

AUGUST 2016

## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Phantom limb pain (PLP) is pain that is experienced in a missing or amputated limb. Essentially, patients who experience PLP experience pain in a region of the body that no longer exists (due to amputation) or never existed (for example, in cases of congenital limb deficiency). This is not to be confused with residual limb pain (a.k.a. stump pain), which is pain that is experienced in the remaining part of the limb (Merskey & Bogduk 1994). Currently, there are no medical tests specifically used to diagnose PLP (Mayo Clinic). Instead, physicians can identify this condition based on the patient's medical history and circumstances leading up to the

phantom pain sensations in the affected body region(s). PLP has been described in many different body parts, including upper and lower limbs, breasts, eyes, and genitals (Sherman et al. 1984, Hansen et al. 2011, Rasmussen et al. 2011, Wade & Finger 2010). The suffering and trouble caused by PLP has been described as “moderate” to “very much” in 65% of patients (Kooijman et al. 2000), with just under 70% rating typical PLP at moderate to severe levels (between 4-10 on a 0-10 numerical rating scale; Sherman et al. 1984). Descriptions of PLP vary including stabbing, electric shock-like, pins and needles, tingling, squeezing/crushing (Sherman et al. 1984; Wartan et al.1997).

## Prevalence

Not all patients with an amputation or missing limb will experience PLP. Estimates on the prevalence of PLP have ranged from roughly 50-80% of amputees (Sherman et al. 1984, Kooijman et al. 2000, Wartan et al. 1997, Houghton et al 1994), with significantly lower numbers (~4%) being reported for patients with congenital limb deficiency (Wilkins et al. 1998). Moreover, because the number of individuals undergoing limb amputation is expected to grow over time in the US (Ziegler-Graham et al. 2008), the sheer number of patients experiencing PLP will undoubtedly grow in parallel. According to 2005 national estimates, there were 1.6 million people with limb loss, and those numbers are expected to at least double by 2050 (Ziegler-Graham et al. 2008).

## Current Therapies

Both pharmacologic and non-pharmacologic treatments are currently used for managing PLP. Overall evidence for pharmacologic interventions is mixed on efficacy, while mind-body therapies – while promising – would benefit from greater study and follow-up of patients over time. This section will cover the more common therapies found in these domains.

### Pharmacologic treatments

Available pharmacotherapies for PLP patients widely vary because there is no one mechanism that is consistently thought to be solely responsible for generating PLP. Therefore, drug targets are derived based on the current understanding of what particular mechanisms may be involved in generating PLP. Currently, a few different peripheral and central mechanisms are proposed to underlie PLP, which includes changes induced by neuromas that develop post-amputation, changes in the spinal cord at the dorsal horn, as well as cortical reorganization in somatosensory cortex (Flor et al. 2006; McCormick et al. 2014; Subedi & Grossberg 2011). Drugs acting on peripheral mechanisms typically inhibit nerve impulses, which includes bupivacaine and ropivacaine. However, there is mixed evidence for their efficacy in treating PLP (McCormick et al. 2014). Amitriptyline, a tricyclic antidepressant which is thought to have peripheral analgesic effects, has also been used with moderate to no effect on PLP (Alviar et al. 2011; McCormick et al. 2014). Opioids are also sometimes used, which has been moderately to highly successful in reducing PLP short-term (Alviar et al. 2011). There has also been some research to prevent the development of PLP with an epidural administration of an opioid and nerve blocks just before amputation (preemptive analgesia). This, however, has

also shown mixed efficacy across studies (McCormick et al. 2014). Botulinum toxin Type A injections at the site of the residual limb have also been explored, but the evidence for relieving PLP has been weak or restricted to small sample sizes (Wu et al. 2012; Jin et al. 2009).

Central mechanisms responsible for PLP point to neuroplastic changes at the dorsal horn and somatosensory cortex. For example, the dorsal horn shows evidence of sensitization after amputation as well as spinal reorganization of afferent signals in this region (Flor et al. 2006). Reorganization at the somatosensory cortex may also contribute to PLP. After amputation, the somatosensory region responsible for representing the amputated limb no longer serves a functional purpose; therefore, adjacent somatosensory regions “invade” leading to abnormal circuitry that may lead to the development of PLP. Treatments targeting central mechanisms are typically antiepileptic drugs (AEDs) to counteract hyperexcitability in the central nervous system. Evidence for the efficacy of AEDs (particularly gabapentin and topiramate) – while promising – is mixed (Alviar et al 2011; McCormick et al. 2014).

### **Non-pharmacologic treatments**

There is some literature to suggest that mind-body therapies may provide some benefit to treating PLP. Mind-body therapies take advantage of the connection between the mind and body by trying to alter physical functioning and experience (i.e., pain) through mind and behavior. While literature is sparse in the use of mind-body therapies for specifically treating PLP (Moura et al. 2012), the ones most commonly found were mirror visual feedback therapy, guided imagery, hypnosis, and biofeedback techniques.

Mirror visual feedback therapy has been most well-studied out of all mind-body therapies to specifically treat PLP. Traditionally, this therapy involves a patient placing their non-amputated limb into a box containing mirrors which then gives the perception that the amputated limb has been restored (Ramachandran & Altschuler 2009). However, there are also studies that have effectively used virtual feedback to give the perception of limb restoration and functionality (Mercier & Sirigu 2009). While visual feedback therapy has been found to alleviate PLP to some degree, evidence from randomized trials is relatively sparse (Chan et al. 2007) with most evidence coming from case series/reports or non-randomized trials (Moura et al. 2012).

Guided imagery techniques have also been used for treating PLP, which requires patients to immerse themselves into their senses through mental imagery and imagination. In the case of PLP, this often means using mental imagery on the phantom limb to imagine sensations or movement to alleviate pain. Evidence for the efficacy of this technique, while showing some promise, is sparse (Moura et al. 2012).

There are a few studies using hypnosis for treating PLP with some efficacy, but again, studies are also sparse for this technique and could benefit from more rigorous study (Moura et al. 2012). Lastly, biofeedback therapy (involves using biofeedback instruments to bring to

awareness autonomic nervous system dysregulation) has some data on reducing PLP (Moura et al. 2012). However, very few studies of this type exist and are underpowered.

## Pre-Clinical Research

No preclinical evidence was found regarding the use of cannabis to specifically treat PLP. While preclinical studies investigating the effects of cannabis and cannabinoids on pain is found in the literature, these studies group PLP under neuropathic pain which makes any interpretation of treatment efficacy nearly impossible without concerted efforts to stratify results by this patient group.

## Clinical Trials

As of mid-August 2016, only one clinical trial has been identified that examines the efficacy of cannabinoids on specifically treating PLP. However, this study – while listed as completed on the website – has not been updated on ClinicalTrials.gov to include study results, nor have any publications been found relating to this study. This particular study was a randomized, double-blind clinical trial investigating the effects of nabilone (Cesemet; synthetic analogue of THC) on the management of pain and quality of life in phantom limb patients. Study participants were assigned nabilone or placebo (parallel assignment) with primary and secondary measures collected at baseline, 2, 4, and 6 weeks of treatment. The primary outcome measure was scores on the visual analogue scale for pain. Secondary outcome measures were scores on 1) Depression Anxiety and Stress Scale, 2) Groningen Sleep Quality Scale, 3) SF-36, 4) frequency of phantom limb pain, and 4) daily prosthetic wearing time. Study details can be found at [Nabilone for the Treatment of Phantom Limb Pain](https://clinicaltrials.gov/show/NCT00699634) <https://clinicaltrials.gov/show/NCT00699634>

## Observational Studies

No observational studies have been identified that specifically address pain management in PLP patients with cannabis. While there are several studies investigating the effects of cannabis and cannabinoids on neuropathic pain patients, many of these studies do not stratify their results by neuropathic pain type/cause (i.e., PLP). Therefore, there is a gap in knowledge within this particular patient group.

There is one survey study by Dunn and Davis (1974) that did measure the effects of cannabis on PLP in spinal cord injured males. Of the nine (out of 10) patients experiencing phantom pain, four (44%) experienced a decrease in PLP, while one patient (11%) showed an increase in PLP. Another two patients (22%) showed no effect of cannabis on PLP, while another two (22%) indicated that cannabis helped distract from PLP while not reducing actual PLP. However, it should be noted that this was an informal survey conducted on a small sample within one hospital in the US. Details on survey methodology were also omitted in this publication. Lastly, because the patient sample all had spinal cord injuries, results are even further restricted to apply to an even smaller subset of PLP patients (PLP patients with spinal cord injuries).

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of PLP were found.

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Post-traumatic Stress Disorder (PTSD)

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## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Post-traumatic stress disorder (PTSD; both "post-traumatic" and "posttraumatic" are used in different sources) is a mental disorder that evokes severe distress, chronic suffering and impairment. Its core symptoms comprise re-experiencing traumatic content, persistent avoidance of traumatic content, negative alterations in cognitions, and arousal and reactivity (American Psychiatric Association 2013). This condition causes significant occupational, medical, and psychosocial disability, and its consequences are enormously costly, not only to

the survivors and their family, but also to the health care system and society. Work impairment associated with PTSD is similar to the amount of work impairment associated with major depression (Brunello 2001).

The Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the 2013 update to the American Psychiatric Association’s classification and diagnostic tool. In the U.S. the DSM serves as the primary authority for psychiatric diagnosis. In prior editions of the DSM PTSD was grouped under anxiety disorders. In DSM-5 PTSD is no longer classified as an anxiety disorder, but instead falls under a new chapter, “Trauma- and Stressor-Related Disorders.” In addition to this change of conceptualization and categorization, several changes were made in the diagnostic criteria. In order to be diagnosed with PTSD according to the DSM-5, a person needs to fill Criteria A through H, what is presented here summarizes the DSM-5 criteria (American Psychiatric Association 2013):

**Criterion A** – a person was exposed to one or more event(s) that involved death or threatened death, actual or threatened serious injury, or threatened sexual violation. In addition, these events were experienced in one or more of the following ways:

1. The event was experienced by the person
2. The event was witnessed by the person as it occurred to someone else
3. The person learned about an event where a close relative or friend experienced an actual or threatened violent or accidental death
4. The experienced repeated exposure to distressing details of an event, such as a police officer repeatedly hearing details about child sexual abuse

**Criterion B** – A person experiences at least one of the following intrusive symptoms associated with the traumatic event:

1. Reoccurring, involuntary, and intrusive upsetting memories of the traumatic event
2. Repeated upsetting dreams where the content of the dreams is related to the traumatic event
3. The experience of some types of dissociation (for example, flashbacks) where the person feels as though the traumatic event is happening again
4. Strong and persistent distress upon exposure to cues that are either inside or outside of a person’s body that are connected to the person’s traumatic event
5. Strong bodily reactions (for example, increased heart rate) upon exposure to a reminder of the traumatic event

**Criterion C** – Frequent avoidance of reminders associated with the traumatic event, as demonstrated by one of the following:

1. Avoidance of thoughts, feelings, or physical sensations that bring up memories of the traumatic event
2. Avoidance of people, places, conversations, activities, objects, or situations that bring up memories of the traumatic event

**Criterion D** – At least two of the following negative changes in thoughts and mood that occurred or worsened following the experience of the traumatic event:

1. The inability to remember an important aspect of the traumatic event
2. Persistent and elevated negative evaluations about one’s self, others, or the world (for example, “I am unlovable,” or “The world is an evil place”)
3. Elevated self-blame or blame of others about the cause or consequence of a traumatic event
4. A negative emotional state (for example, shame, anger, fear) that is pervasive
5. Loss of interest in activities that one used to enjoy
6. Feeling detached from others
7. The inability to experience positive emotions (for example, happiness, love, joy)

**Criterion E** – At least two of the following changes in arousal that started or worsened following the experience of a traumatic event:

1. Irritability or aggressive behavior
2. Impulsive or self-destructive behavior
3. Feeling constantly “on guard” or like danger is lurking around every corner (or hypervigilance)
4. Heightened startle response
5. Difficulty concentrating
6. Problems sleeping

**Criterion F** – the above symptoms last for more than one month

**Criterion G** – The symptoms bring about considerable distress and/or interfere greatly with a number of different areas of a person’s life.

**Criterion H** – The symptoms are not due to a separate medical condition or some form of substance use.

## **Prevalence**

A nationally representative face-to-face household survey of adult conducted in 2001-2003 using a fully structured diagnostic interview found 3.5% of the US adult population met DSM-IV criteria for PTSD (Kessler 2005). As part of an assessment of psychiatric morbidity among adults in England participants completed a screening tool for PTSD. The screening tool is aligned with some DSM-IV criteria categories, but authors indicate positive screening is likely to over-estimate PTSD prevalence based on a full clinical assessment. A total of 3.0% screened positive for PTSD, with a positive screening test decreasing from 4.7% among 16-24 year olds to 0.6% of adults aged 75 and over. No significant gender difference was found (McManus 2008).

Lifetime prevalence of PTSD has been estimated at 7.8%. Among groups at higher risk prevalence is higher. It has been estimated at over 50% among survivors of rape (Kessler 1995).

## Current Therapies

Clinical practice guidelines are generally consistent in recommending certain forms of trauma-focused psychotherapy as first-line therapy for PTSD. The methods with most evidence of effectiveness are cognitive behavioral therapies (CBT), exposure therapy, and eye movement desensitization and reprocessing (EMDR) (Forbes 2010, VA/DoD PTSD guideline 2010). Though there is evidence that these psychotherapies have beneficial effects for some PTSD patients (Bradley 2005, Cloitre 2009, Steenkamp 2015, VA/DoD PTSD guideline 2010, Watts 2013), meta-analyses of clinical trials of these methods indicate the proportion of PTSD patients that achieve clinically significant symptom improvement is approximately 50% (Bradley 2005, Steenkamp 2015) and those with clinically significant symptom improvement often still have a substantial symptom burden (Bradley 2005). There is concern that the expansive exclusion criteria in most clinical trials of therapy for PTSD limit the degree to which their results can be generalized to the full range of persons with PTSD (Bradley 2005, Schottenbauer 2008). For example, in a review and meta-analysis of 26 studies of psychotherapy for PTSD the authors found that 46% of the studies excluded patients for suicide risk, 62% excluded patients for drug or alcohol use, and 62% used some version of “serious comorbidity” as an exclusion criterion (Bradley 2005). Interpretation of clinical trial results is complicated by a relatively high dropout rate (typically in range of 25 to 30%) that often isn’t fully accounted for in analyses (Bradley 2005, Cloitre 2009, Schottenbauer 2008, Steenkamp 2015). Little is known about persistence of symptom improvement over time (Bradley 2005, Steenkamp 2015).

There is evidence of effectiveness of some pharmaceutical agents in treating PTSD, but their role appears to be secondary to psychotherapy. A recent meta-analysis of pharmacotherapy for PTSD commissioned by the World Health Organization assessed 51 randomized controlled trials. The authors found evidence of effectiveness for some selective serotonin reuptake inhibitors (SSRIs), but with relatively small effect sizes whose clinical relevance is unclear (Hoskins 2015). Authors of another meta-analysis reached a tentative conclusion that psychotherapy may be more effective than medication for the treatment of PTSD (Watts 2013). Most current clinical guidelines for treatment of PTSD consider medication a second-line therapy (Forbes 2010, VA/DoD PTSD guideline 2010). A Cochrane Collaboration review published in 2010 concluded there is not enough evidence available to support refute the effectiveness of combined psychological therapy and pharmacotherapy compared to either of these interventions alone (Hetrick 2010).

Among authors of review articles and meta-analyses of therapies for PTSD patients there is widespread agreement that on the need for improvement in existing PTSD treatments as well as the development and testing of novel evidence-based treatment strategies (Bradley 2005, Brunello 2001, Hetrick 2010, Hoskins 2015, Steenkamp 2015).

## Pre-Clinical Research

There are numerous published articles on laboratory and animal research studies with findings likely relevant to PTSD. Presented here are just a few. de Bitencourt (2013) was chosen because it is a review article that covers many of these studies. Rabinak (2013) and Das (2013) were chosen because they present human models likely relevant to PTSD.

**de Bitencourt RM, Pamplona FA, Takahashi RN. A current overview of cannabinoids and glucocorticoids in facilitating extinction of aversive memories: Potential extinction enhancers. *Neuropharm* 2013;64:389-395.**

This paper outlines animal models of fear extinction and describes how these models have been used to examine the potential of extinction enhancing agents which specifically alter the endocannabinoid and glucocorticoid systems. Fear extinction is the gradual reduction in fear responses when an animal or person is exposed to a stimulus that once evoked a fear reaction.

There are a variety of methods of studying fear conditioning in animals, but they typically use a classic fear conditioning protocol. In this protocol, a previously neutral conditioned stimulus (CS) is paired with an unconditioned stimulus (US) such as a foot shock. In this method a scientist will play a tone (CS) before mildly electrocuting a rat's foot. Eventually, exposing the rat to only the US (e.g. the tone) without the CS (foot shock) will cause the rat to express fear behavior, hormonal changes, and other physiological responses. During extinction, conditioned fear response gradually decreases through re-learning with repeated omission of the aversive stimulus. Conditioned fear is also studied with operant conditioning paradigms, in which the US presentation occurs when the animal expresses (or refuses to express) a given behavior.

The review cites 16 studies that affirm the important role of the endocannabinoid system in the extinction of aversive memories, including several that showed stimulation of the CB1 receptors facilitated fear extinction. The final section of the paper concludes with a summary of the studies showing interaction between the glucocorticoid system and the endocannabinoid system.

**Rabinak CA, Angstadt M, Sripada CS, Abelson JL, Liberzon I, Milad MR, Phan KL. Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology* 2013;64:396-402.**

A first-line approach to treat anxiety disorders is exposure-based therapy, which relies on extinction processes such as repeatedly exposing the patient to stimuli associated with the traumatic, fear-related memory. However, a significant number of patients fail to maintain their gains, partly attributed to the fact that this inhibitory learning and its maintenance is temporary and conditioned fear responses can return. This randomized, double-blind, placebo-controlled, between-subjects study was designed to test the impact of THC on fear extinction in humans. Animal studies had previously shown that activation of the cannabinoid system during

extinction learning enhances fear extinction and its retention. Specifically, CB1 receptor agonists such as THC had been shown in animal studies to facilitate extinction recall by preventing recovery of extinguished fear in rats. However, this phenomenon had not been investigated in humans. Twenty-nine healthy volunteers age 21-45 were recruited and randomized to receive either THC (7.5 mg MARINOL) or placebo on day 2 of a 3-day Pavlovian fear extinction paradigm with skin conductance response used to measure conditioned-fear responses and extinction learning:

- Day 1: Fear Acquisition
  - Participants sat at a computer with headphones. The subject would be shown colored boxes of three different colors, one box at a time for 4 seconds each. A loud noise was played when blue and yellow boxes were displayed, but not when red boxes were shown.
- Day 2: Extinction Learning
  - The computer displayed only blue boxes and red boxes; no loud noise was played.
- Day 3: Extinction Memory Recall Test
  - To assess extinction memory learning, boxes of all three colors were displayed. No loud noise was played.

Results showed evidence that pre-extinction administration of THC facilitates extinction of conditioned fear in humans. Participants that had received placebo during extinction learning exhibited spontaneous recovery of fear at appearance of the blue box on day 3 – fear that had been extinguished on day 2. Patients who received THC on day 2 experienced less of the spontaneous recovery of fear. Notably, THC did not affect extinction learning during day 2, but only decreased spontaneous recovery of fear.

**Das RK, Kamboj SK, Ramadas M, Yogan K, Gupta V, Redman E, Morgan CJ. Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology* 2013;226:781-792.**

This is the first study of whether cannabidiol (CBD) facilitates extinction learning in humans. Forty-eight healthy volunteers, age 18-35, were recruited for this double-blind, placebo-controlled between-subjects study in which a Pavlovian fear-conditioning paradigm was used. Participants were divided into one of three groups: CBD pre-extinction and placebo post-extinction, placebo pre-extinction and CBD post-extinction, and placebo pre-extinction and post-extinction.

#### Day 1: Conditioning and Extinction

##### 1. Conditioning

- a. In a computer simulation, participants were repeatedly shown two different-colored boxes, one at a time. Boxes of only one of the two colors would be accompanied by a shock a set percentage of the time.
- b. Throughout the presentations, shock expectancy ratings (0 to 5 scale of certainty) and skin conductance response were measured, as well as Mood Rating Scale (MRS) and Bodily Symptom Scale (BSS).

## 2. Extinction

- a. CBD pre-extinction group inhales CBD; other two groups inhale placebo
- b. Repeated presentation of the two colors of boxes, one at a time – this time with no shocks
- c. Throughout the presentations, shock expectancy ratings (0 to 5 scale of certainty) and skin conductance response were measured, as well as MRS and BSS.
- d. CBD-post-extinction group inhales CBD; other two groups inhale placebo

### Day 2: Recall and Reinstatement

1. Repeated presentations of the boxes, in different contexts – both before (recall) and after (reinstatement) shocks were once again used with boxes of the one color.
2. Throughout the presentations, shock expectancy ratings (0 to 5 scale of certainty) and skin conductance response were measured, as well as MRS and BSS.

CBD given post-extinction enhanced consolidation of extinction learning as assessed by shock expectancy. CBD administered at either time produced trend level reduction in reinstatement of autonomic contextual responding. No acute effects of CBD were found on extinction. The authors conclude the findings provide evidence that CBD can enhance consolidation of extinction learning in humans and suggest that CBD may have potential as an adjunct to extinction-based therapies for anxiety disorders such as PTSD.

## Clinical Trials

No randomized, controlled clinical trials have been completed for cannabis product therapy in PTSD patients. Two such trials are now being organized. The primary investigator for the larger of the two is Marcel Bonn-Miller from the Department of Psychiatry at the University of Pennsylvania and the VA National Center for PTSD. Three types of smoked cannabis (high THC; high CBD, high THC/high CBD) will be compared with each other and to placebo in alleviating symptoms and occurrence of adverse events among 76 U.S. veterans with treatment-resistant PTSD. Investigators plan to begin this study in the summer of 2016 with an estimated completion date of September, 2018. This study has funding from the state of Colorado's pool of money to support research, derived from taxes on retail marijuana. [Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment-Resistant PTSD](#)

(<https://clinicaltrials.gov/ct2/show/NCT02759185?term=PTSD+cannabis&rank=1>.)

The second trial, a triple-blinded cross-over study will compare three types of vaporized marijuana (high THC/low CBD; high THC/high CBD; low THC/low CBD) with each other and with to placebo in alleviating symptoms and occurrence of adverse events among 42 patients with treatment-resistant PTSD. Investigators plan to begin this study in the summer of 2016 with a December, 2016 estimated completion date. The sponsor for this study is Tilray, a Canadian marijuana producer. [Evaluating Safety and Efficacy of Cannabis in Participants With Chronic Posttraumatic Stress Disorder](#)

(<https://clinicaltrials.gov/ct2/show/NCT02517424?term=PTSD+cannabis&rank=2>).

**Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral  $\Delta 9$ -tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation* 2014, 34:587-591.**

This small, short-term, open-label (no control group) study assessed the safety and benefit of THC administered under the tongue. Ten adults with PTSD diagnosed > 1 year and < 3 years since the traumatic event were recruited at one outpatient clinic in Israel. Seven were men, average age was 52, and the traumatic event was war-related in 5, road accident in 3 and assault/rape in 2. All were receiving stable psychotropic medication for at least 4 weeks, with an average of more than four different medications. They remained on their stable regimen throughout the three week study. Outcome measures included Clinician-Administered PTSD Scale total score and three component scores, the Clinical Global Impression-Severity Scale (7 point scale from 1 “normal” to 7 “amongst the most severely ill patients”), Clinical Global Impression-Improvement Scale (7 point scale from 1 “very much improved”) through 7 (“very much worse”), Pittsburgh Sleep Quality Index, Nightmare Frequency Questionnaire, and Nightmare Effects Survey. The THC was mixed with olive oil to achieve 2.5 mg/1 cc. Patients were instructed to take 1 cc under the tongue twice per day. After two days each was contacted by a study clinician to assess side effects. If well tolerated, the dose was increased to 2 cc twice per day (5 mg THC twice per day) and remained at that level. All patients went to the higher dose. Mild side effects were reported by four participants (dry mouth, headache, and dizziness); no participants stopped treatment because of side effects. Statistically significant improvement between baseline and end of study was seen for PTSD hyperarousal component score, both CGI-S and CGI-I, sleep quality, nightmare frequency, and nightmare effects. As the authors acknowledge, lack of a control group makes it difficult to determine whether the changes observed were due to oral THC or to variability in the course of PTSD or expectancy (placebo) effect. The study’s small size and short duration are additional important limitations.

## Observational Studies

**Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *J Psychoactive Drugs* 2014;46:73-77.**

Retrospective study of the first 80 patients evaluated by one of the authors (Greer) for participation in the New Mexico Department of Health’s Medical Cannabis Program for PTSD. In the article Greer explains that he was deluged with requests to be evaluated, so he set up a telephone screening process to prioritize who he would see. The screening process was developed around DSM-4 criteria for PTSD: “(1) the experience of and emotional response to a trauma that met the DSM-IV Criterion A for PTSD, (2) the presence of several of the major symptoms in Criteria B, C, and D (re-experiencing, avoidance, and hyperarousal) of PTSD when not using cannabis; (3) significant relief of several major PTSD symptoms when using cannabis; and (4) lack of any harm or problems in functioning resulting from cannabis use. All patients who met these screening criteria were evaluated. These were people who had found benefit in using marijuana for PTSD and were now looking for legal protection for their use. As part of the evaluation, patients were asked to think about their PTSD symptoms in the past and to fill out

the Clinician Administered Posttraumatic Scale for DSM-IV (CAPS) form twice: once for when they were using marijuana and once for when they were not using marijuana.

It is unclear what other information, if any, was collected from medical records, though the article notes duration of time periods off cannabis were not collected. When scores were compared, there was a 75% reduction in scores, for each of the three categories of PTSD symptoms and overall, when comparing periods of use vs. non-use of cannabis. As the authors note, a big caveat of these results, is that it was a carefully selected group of patients who expressed their belief that prior cannabis use helped their PTSD symptoms. There is potential for biased responses in order to get approved for the state marijuana program. The authors present some evidence in support of the proposition that there was not a lot of bias of this sort. Another concern is that when patients responded to the CAPS for when they were not using marijuana, they could have been thinking of days immediately after they stopped using, when they could have been experiencing withdrawal side effects, some of which overlap with PTSD symptoms. The impact of this would be to exaggerate the difference in CAPS scores between periods of marijuana use and non-use. The authors' conclusion: "Because only patients who reported benefits from cannabis in reducing their PTSD were studied, no conclusions can be drawn as to what proportion or type of PTSD patients would benefit from treatment with cannabis or its constituents."

**Bremner, D. J., Southwick, S. M., Darnell, A., & Charney, D. S. (1996). Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. *American Journal of Psychiatry* 1996;153:369-375.**

In this retrospective, longitudinal study, Vietnam War veterans were studied to observe the natural course of their PTSD symptoms in the twenty plus years after the war. All 61 veterans involved in the study had combat experience and were interviewed during an inpatient stay for PTSD treatment during the early 1990s. Assessment tools gathered, for two-year intervals, presence of a list of PTSD symptoms; abuse of alcohol, marijuana (abuse not clearly defined), heroin, benzodiazepines, and cocaine; and perceptions of relief and exacerbation of PTSD symptoms by these drugs. Interviews collected retrospective data on the veterans' experiences in the two years preceding their war experience, during the war, and after their combat experience through 1992.

Compared to the two-year, pre-combat period, there was a significant increase in alcohol, marijuana, and cocaine abuse during the war and in all five of the drug categories studied in the years immediately after their combat experience, consistent with the belief that at least some use of these drugs in PTSD patients is self-medication of symptoms. Participants in general found alcohol and heroin helpful for PTSD symptoms in the hyperarousal and intrusive categories and benzodiazepines and marijuana helpful for hyperarousal symptoms, while cocaine had a tendency to worsen symptoms in the hyperarousal category.

Caution must be taken when interpreting these results, since the authors acknowledge multiple factors that confound the data and that limit the findings' generalizability. For instance, PTSD patients with noncombat traumas, such as childhood abuse, may have a

different symptom progression from combat veterans. And, despite methodology to help participants recall the nature of timing and symptoms years ago, some of those recollections might have been inaccurate. While the findings are consistent with the hypothesis that PTSD patients self-medicate with alcohol and other substances, it is possible that alcohol and substance abuse occurred independently from PTSD symptom progression. Only association and not causation can be assessed with this study.

**Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *The Journal of Clinical Psychiatry* 2015;76:1174-1180.**

American veterans diagnosed with PTSD and admitted to specialized Veterans Affairs PTSD treatment programs from 1992 to 2011 were included in this study (n=12,770; mean age=51.7 years; 96.7% male). Documentation at admission of consuming 2 or more drinks per occasion and use of any illicit drugs other than marijuana during the 30 days prior to admission excluded 34,540 of 47,310 potential participants (73%). Use of marijuana, alcohol, and other drugs, PTSD symptom severity, co-morbid psychiatric diagnoses, PTSD treatment program characteristics, community adjustment variables, and demographics were collected at program admission. Use of marijuana, alcohol abuse, abuse of other drugs, PTSD symptom severity, employment status and violent behavior were assessed at 4 months after discharge.

The 12,770 study subjects were divided into four groups based on marijuana use at admission and at four months after discharge: Never Users (89%), Stoppers (2% - use at admission, but not at four months post-discharge), Continuing users (2%) and Starters (7% - no use at admission, but use at 4 months post-discharge).

The authors describe several statistically significant findings. Higher measures of symptom severity at four months post-discharge were observed among Starters and Continuing Users compared to Never Users and Stoppers. Continuing Users had shorter lengths of stay in treatment programs compared to Never-Users and Stoppers. Starters showed higher measures of violent behavior at follow up compared to all other groups.

Though the authors say the findings suggest marijuana use may worsen PTSD symptoms or nullify the benefits of specialized intensive treatment, they acknowledge the results could also mean PTSD patients refractory to treatment are more likely to use marijuana in an attempt to self-medicate. Though this study is longitudinal, it shows only associations and cannot determine causation (again, as admitted by the authors). Violence was measured on a narrow scale, ranging from 0 (least violent) to 4 (most violent). And at 4 months post-discharge the four groups had a narrow range of mean scores: Starters = 1.25; Continuing Users = 0.93; Never-Users = 0.87; Stoppers = 0.76. The score for Starters was statistically significantly higher than for the other groups, but it is not clear how meaningful the difference between 1.25 and the other scores is. In addition, Starters had more frequent alcohol abuse than the other groups 4 months post-discharge (which is related to violence).

There are a few additional limitations to interpreting the results. Analyses adjusted for measured differences among groups at baseline but it is quite possible unmeasured differences

could have resulted in biased results. Perceptions of short-term symptom relief from cannabis were not assessed. The ability to generalize the results to all veteran PTSD patients is limited by subjects being admitted to specialized treatment programs and by excluding 73% of such patients because of alcohol use and use of illicit drugs other than marijuana.

**Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. *Drug and Alcohol Dependence* 2014;136:162-165.**

Why do patients with PTSD use medicinal cannabis compared to patients who do not have PTSD? Is the interaction between PTSD and PTSD-specific, cannabis-use motivations associated with more frequent use of medicinal cannabis? These questions were the authors' focus in this study.

To answer these questions, 170 adults who obtained their medicinal cannabis from a single dispensary in San Francisco were studied. Each participant completed the PTSD checklist – Civilian Version, a 17-item questionnaire where respondents indicate the presence and severity of PTSD symptoms. Following recommendations of community samples, a score of 30 was used as a cut-off to form two groups, those without PTSD and those with probable PTSD. Participants also filled out questionnaires about frequency of cannabis use in the past 30 days and motivation for cannabis use. For the cannabis use questionnaire respondents rated how often they used cannabis (5-point scale: 1=almost never/never to 5=almost always/always) for each of 36 reasons, comprising 12 domains (enjoyment, conformity, coping, experimentation, boredom, alcohol, celebration, altered perception, social anxiety, low risk, sleep, and availability).

Analysis showed that individuals with probable PTSD reported greater motivation to use cannabis for sleep and coping reasons compared to those without PTSD. No association was found between PTSD and any of the other use motivations. Hierarchical regression also demonstrated that sleep motivation predicted past 30-day cannabis use frequency. But, being in the probable PTSD group did not predict past 30-day cannabis use frequency.

The authors noted several important limitations to their study. First, cause-effect conclusions cannot be drawn from a cross-sectional design. The study sample was narrow: mostly male patients from a single dispensary in San Francisco limits the findings' generalizability. Data were self-reported, so they are potentially biased. Last, volunteers were not diagnosed with PTSD, and behavioral/interview-based verification of symptom severity was not conducted.

**Bonn-Miller MO, Babson KA, Vujanovic AA, Feldner MT, Sleep problems and PTSD symptoms interact to predict marijuana use coping motives: A preliminary investigation. *J Dual Diagnosis* 2010;6:111-122.**

In this study, Bonn-Miller, Babson et al. aimed to uncover what factors affect the association between PTSD and coping-motivated cannabis use. They hypothesized that greater sleep difficulties and more severe PTSD symptoms (excluding sleep problems) are associated

with higher levels of coping-motivated cannabis use and that the interaction between sleep problems and PTSD symptom severity would be greater than either factor alone. Participants were recruited through newspaper advertisements, flyers, and announcements that described a laboratory study on “stressful life events.” Twenty (mean age = 34 years; 75% female) met DSM-IV criteria for PTSD and were currently using marijuana (past 30 days); this group formed the study cohort. Validated tools were used to collect information on sleep quality and motivations for marijuana use.

Using multiple hierarchical regression, a statistically significant, positive association between sleep difficulties and the degree of coping motivations was observed. However, the regression analysis did not reveal a statistically significant, direct relationship between symptom severity and coping-motivated cannabis use. Results showed a statistically significant interaction between sleep difficulties and symptom severity beyond the main effects of each. This interaction occurred independently of symptom severity. Neither symptom severity nor sleep problems were related to other motivations of cannabis use, such as social or conformity motivations. The authors conclude, “These findings highlight sleep problems as the primary driving force of the interaction, suggesting that individuals at highest risk for using marijuana for coping reasons are those with high levels of sleep problems.”

The authors acknowledge the limitations of this study: small, mostly female study sample; cross-sectional design that precludes assessing temporal relationship among PTSD symptom severity, sleep problems, and coping-oriented marijuana use; and self-report measurements (especially sleep quality). They describe need for a larger study of prospective design with direct observation of sleep to replicate and extend the findings of this study.

**Bonn-Miller MO, Vujanovic AA, Drescher KD. Cannabis use among military veterans after residential treatment for posttraumatic stress disorder. *Psychology of Addictive Behaviors* 2011;25:485-491.**

This paper studied substance use patterns after treatment discharge among 432 male Veterans admitted to a VA residential rehabilitation program for PTSD. The program admits veterans with severe PTSD symptoms that have not been successfully ameliorated with inpatient treatment. The veterans are required to be free of substance use at least 15 days prior to admission. The authors hypothesized that lower levels of change in PTSD symptom severity between treatment intake and discharge would significantly predict higher frequency of cannabis use 4 months after discharge.

To test this hypothesis, data on PTSD symptom severity and substance use (alcohol, cannabis, cocaine, opiates, amphetamines) were collected at admission and discharge from the residential treatment program and four months after discharge. 8.1% reported cannabis use during the 2 months prior to admission and 54.3% of these were again using cannabis 4 months after discharge. Among the 92% not using cannabis during the 2 months prior to admission 10.1% were using it 4 months after discharge. Using linear regression, several findings were reported. Lower levels of symptom improvement between intake and discharge predicted greater cannabis use four-month after discharge in a statistically significant manner. Frequency

of cannabis use during the two months preceding intake in the program predicted cannabis use at the four-month follow-up. Smaller levels of improvement in PTSD avoidance/numbing and hyperarousal symptom severity were observed to incrementally predict cannabis use at follow-up in a statistically significant way.

Based on these findings, the authors hypothesized that veterans with lower symptom improvement may use cannabis as an alternative method of coping. The study's results suggest that veterans with high levels of hyperarousal symptoms, such as irritability or sleep disturbance, may be especially likely to consume cannabis.

However, several factors confound these findings and interpretations. Structured diagnostic interviews were not conducted, so study participants may have had other mental-health or personality disorders. Data collection and veterans' benefits eligibility determination were conducted at the same facility, leading to possible bias in veterans' self-reported symptom severity and substance consumption. Only combat-exposure trauma was studied, so findings may not apply to other kinds of trauma. Only male veterans were studied. Finally, substance use severity (e.g., substance use or dependence, drug potency, etc.) was not examined

**Bonn-Miller MO, Vujanovic AA, Feldner MT, Bernstein A Zvolensky MJ. Posttraumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *J Traumatic Stress* 2007;20:577-586.**

What motivates people with posttraumatic stress symptoms to use cannabis was investigated in this cross-sectional study. This study included community-recruited volunteers from a Vermont college town who were current cannabis smokers and had experienced a traumatic event, as defined by the DSM-IV. The authors hypothesized that more severe symptoms would be associated with higher levels of coping-motivated use, even when accounting for the level of participants' levels of cannabis, cigarette, and alcohol consumption. They further hypothesized that no other motivations would be associated with symptom severity.

Using hierarchical linear regression analysis, the authors confirmed their three hypotheses. Interestingly, they also found no evidence linking posttraumatic stress symptoms to the frequency of cannabis use in the past thirty days.

A number of confounding factors limit these findings, however, the authors note. First, the method of recruitment and screening participants may limit the variability of posttraumatic stress symptoms. Study participants were demographically homogenous (young; mean age = 19.4 years) and experienced a narrow range of life traumas, limiting the generalizability of the findings. Results were vulnerable to reporting errors, since data were collected from participant self-reports. Importantly, volunteers with traumatic events were studied; participants were not required to be diagnosed with PTSD.

## **National Medical Organization Recommendations**

## American Psychiatric Association

“Because of the lack of any credible studies demonstrating clinical effectiveness, the APA cannot endorse the use of medical marijuana for the treatment of post-traumatic stress disorder (PTSD). The Council on Research and Quality Care reviewed available evidence regarding the use of marijuana in the treatment of PTSD (1-6) and concluded that no published evidence of sufficient quality exists in the medical literature to support the practice.” (Approved by APA Board of Trustees July 20, 2013).

1. Campos-Outcall D et al. Medical Marijuana for the treatment of post-traumatic stress disorder: An evidence review. Mel and Enid Zuckerman College of Public Health. University of Arizona, 2012. (literature reviewed through 2011)
2. Mashiah M. Medical Cannabis as treatment for chronic combat PTSD: Promising results in an open pilot study. Presented at “Patients out of Time” conference, Tucson, AZ, 2012. A double blind study is planned but has not yet been conducted.
3. Grant I et al. Report to the legislature and Governor of the State of California presenting findings pursuant to SB847 which created the CMCR and provided state funding. Center for Medicinal Cannabis Research. UC San Diego. Prepared February 11, 2010.
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## Veterans Administration

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ISSUE BRIEF

Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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# Schizophrenia

AUGUST 2016

## Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

## Definition

Schizophrenia has been identified as a major psychotic disorder for over a century and how it has been conceptualized has evolved over time. It is now understood to have six core domains (Nasrallah 2011):

1. Positive symptoms – including the psychotic symptoms of delusions and hallucinations

2. Disorganization of speech and behavior
3. Negative symptoms – including amotivation and blunt or flat affect
4. Cognitive deficits – including severe impairments in memory, executive functions, and learning
5. Mood symptoms – including depression and suicidal urges as well as hostility and aggression
6. Neuromotor symptoms – including varying degrees of catatonia, stereotypic movements, and dystonia

In its typical course, a prodromal phase with attenuated positive symptoms and declining function appears in late adolescence or early adulthood. Within relatively few years a first psychotic episode heralds the formal onset of schizophrenia. The next decade is generally marked by repeated episodes of psychosis with partial and variable degrees and duration of inter-episode remission with accrual of disability with each episode of illness. Finally, a stable phase or plateau develops, when psychotic symptoms are less prominent and negative symptoms and the stable cognitive deficits increasingly dominate. Recovery of varying amounts can occur at any stage of the illness and, though most patients experience progressive deterioration over time, some show substantial improvement (Tandon 2009).

Schizophrenia is one of the most disabling of psychiatric disorders with profound effects on affected individuals and their families. It is associated with increased likelihood of unemployment and homelessness, with less than one-fifth of affected individuals fully employed (Tandon 2009). Families of patients with schizophrenia, in comparison with families of patients with other chronic diseases, report higher burden and lower support from their social networks and from professionals (Magliano 2005).

## Prevalence

A systematic review of epidemiological studies from multiple countries estimates 7 persons per 1000 will develop schizophrenia during their lifetime. Prevalence is higher among immigrants, in more highly-developed countries, and at high latitude (McGrath 2008). Schizophrenia runs in families and it is estimated that genetic factors contribute around 80% of risk for developing the disease (Nasrallah 2011).

## Current Therapies

The mainstay of current therapy is a wide variety of antipsychotic drugs. These drugs have been shown to have some efficacy at reducing positive symptoms (hallucinations and delusions) and reducing relapse, but produce only limited improvement in negative symptoms, cognitive function, social functioning, and quality of life. Their side effects are often quite troubling, notably neurological movement disorders in the medications introduced in the 1960s and 1970s (examples: chlorpromazine, haloperidol) and metabolic disorders in medications introduced subsequently. Drugs from a variety of classes (anticonvulsants, antidepressants, benzodiazepines, lithium) are used as adjuncts to antipsychotic medications in targeting specific

symptom domains – usually with modest benefits. About a third of patients with schizophrenia continue to suffer from persistent psychotic symptoms despite adequate pharmacotherapy. The limited efficacy of the drugs is exacerbated by the common occurrence of patients not taking their prescribed medications. A comprehensive, multi-modal approach to treatment is recommended, including medication, psychosocial interventions, and assistance with housing and financial sustenance. A variety of psychotherapies and social treatments are used – when tested, they generally show only limited benefit. Finally, there is great variability in how an individual person responds to a particular medication or psychotherapy, so there is an element of trial and error in identifying the best treatments for a specific patient (Tandon 2010).

Though there have been many developments in the treatment of schizophrenia over the past few decades, there remains great need for better therapies. As one recent review summarizes the situation, “The current standard treatments, both pharmacological and psychosocial, remain limited and inadequate as evidenced by partial response and functional disability in the majority of patients at this time ... There is a tremendous need in the pharmacotherapy of schizophrenia including a safer and more effective treatment for positive symptoms, a treatment for negative symptoms, and a treatment for cognitive deficits” (Nasrallah 2011). There is a large volume of research now under way to identify agents and molecular targets to effectively treat the various symptom domains of schizophrenia (Tandon 2010).

## Pre-Clinical Research

Research results published to date make a compelling case for involvement of the endocannabinoid system in schizophrenia, but the nature of that involvement is still quite unclear. Much of the interpretation of pre-clinical study findings remains speculative. The review articles found for this briefing combined discussion of pre-clinical, clinical, and epidemiologic studies and sometimes they include discussion of cannabinoids as both promoters of and therapy for schizophrenia; they are included in the OBSERVATIONAL STUDIES section of this document.

## Clinical Trials

One published clinical trial of a cannabis constituent (CBD) as therapy for schizophrenia was found (Leweke 2012). Three additional clinical trials present on [The Clinical Trials Website](http://www.clinicaltrials.com) www.clinicaltrials.com (one completed and two now recruiting patients) are identified and summarized below.

**Leweke FM, Peimelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012; 2:e94 (7 pages).**

42 patients with acutely exacerbated schizophrenia were randomized to a double-blinded four week trial of oral cannabidiol or the potent antipsychotic drug, amisulpride (dopamine receptor blocker). Enrolled patients were hospitalized for at least the four weeks of the study. Patients

in both groups had significant clinical improvement, with no difference between groups. CBD displayed a much better side effect profile. CBD treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement. “These results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia.”

**[“A Study of GWP42003 as Adjunctive Therapy in the First Line Treatment of Schizophrenia or Related Psychotic Disorder” NCT02006628](https://clinicaltrials.gov/ct2/show/NCT02006628?term=cannabis+schizophrenia&rank=21)**

**<https://clinicaltrials.gov/ct2/show/NCT02006628?term=cannabis+schizophrenia&rank=21>**

This clinical trial is reported as completed in 2015 on [The Clinical Trials Website](http://www.clinicaltrials.gov) www.clinicaltrials.gov. No results are posted on [The Clinical Trials Website](http://www.clinicaltrials.gov) www.clinicaltrials.gov, and results have not been published, but the research sponsor, GWPharma, has announced top-line results. The trial enrolled 88 adults with schizophrenia in the UK, Poland, and Romania. Patients were randomized to 500 mg CBD in oral solution twice daily or placebo in addition to their existing, stable dose of anti-psychotic medication for six weeks of treatment. Primary outcome measures included Positive and Negative Syndrome Scale (PANSS) total score and Positive, Negative, and General subscales, Scale for the Assessment of Negative Symptoms (SANS) score, Clinical Global Impressions – Severity Scale (CGI-S), Clinical Global Impressions – Improvement Scale (CGI-I), and Carer and Participant Global Impression of Change scales (CGIC and PGIC). In September, 2015 GW Pharmaceuticals announced that in the trial cannabidiol showed consistently greater improvement over placebo with respect to PANSS-positive subscale ( $p=0.018$ ), CGI-S ( $p=0.04$ ), and CGI-I ( $p=0.02$ ).

**[“A Four-week Clinical Trial Investigating Efficacy and Safety of Cannabidiol as a Treatment for Acutely Ill Schizophrenic Patients” NCT02088060](https://clinicaltrials.gov/ct2/show/NCT02088060?term=cannabis+schizophrenia&rank=25)**

**<https://clinicaltrials.gov/ct2/show/NCT02088060?term=cannabis+schizophrenia&rank=25>**

This clinical trial is now recruiting patients and has an estimated completion date of December, 2016. An anticipated 150 adults with schizophrenia diagnosis  $\leq 3$  years will be recruited in Denmark and Germany. Patients will be randomized to one of three arms for the four week trial: 1) CBD 300 mg tablets twice/day and placebo olanzapine capsule once/day; 2) Olanzapine capsule 15 mg once/day and placebo CBD tablets twice/day; 3) Placebo CBD tablets twice/day and placebo olanzapine capsule once/day. Primary outcome measure is change in the Positive and Negative Syndrome Scale total score.

**[“Cannabidiol Treatment in Patients With Early Psychosis” NCT02504151](https://clinicaltrials.gov/ct2/show/NCT02504151?term=cannabis+schizophrenia&rank=34)**

**<https://clinicaltrials.gov/ct2/show/NCT02504151?term=cannabis+schizophrenia&rank=34>**

This crossover trial is now recruiting patients and has an estimated completion date of October, 2018. An anticipated 72 adults will be recruited in Connecticut. Patients will be randomized into receive either: 1) treatment with CBD for four weeks followed by two week washout period, followed by four weeks of placebo or 2) placebo for four weeks, followed by a 2 week washout period, followed by four weeks of treatment with CBD. Primary outcome measures

are change in Positive and Negative Syndrome Scale and Clinical Global Impression of Severity scale.

## Observational Studies

Study results presented in reviews of the involvement of the endocannabinoid system (ECS) in psychotic disorders leave little doubt of involvement. However, there is not yet clear understanding of the nature of that involvement. Something that is clearly emerging is the difference in action between THC and CBD, when it comes to the ECS and schizophrenia. Where THC causes acute psychotic effects even in some healthy persons and is implicated in precipitating psychotic disorders and exacerbating psychotic disease, CBD appears to be anti-psychotic, countering the pro-psychotic effects of THC. The presence of both THC and CBD in cannabis – in varying amounts, depending on strain, cultivation, and processing – might be at the heart of confusing scientific signals about the role of cannabis in psychotic disease. To go into the material in detail, the articles and resources discussed below are recommended as a starting point.

**[Information for Health Care Professionals: Cannabis and the cannabinoids.](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf) Health Canada. 2013. [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/marihuana/med/infoprof-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf)**

The “Schizophrenia and psychosis” section (pages 64-65) provides a concise, heavily-referenced discussion of what is known about the involvement of the endocannabinoid system in psychosis, the association of cannabis and THC with psychotic disease and the tantalizing evidence that CBD may have a therapeutic role. The report puts in bold its recommendation regarding whole-plant cannabis products and THC: “The findings presented above and in section 7.7.3 suggest that cannabis use, as well as exposure to  $\Delta^9$ -THC alone, would not be beneficial, and in fact would actually be harmful to those who may be suffering from psychotic disorders, or who may have a genetic predisposition or family history of psychosis or schizophrenia.” Regarding CBD: “The therapeutic potential of CBD alone in the treatment of schizophrenia/psychosis, while promising, requires further study.”

**[Brief Review of Human Studies Regarding Increased Risk of Harm with Cannabis Use \(May, 2016\)](http://www.health.state.mn.us/topics/cannabis/practitioners/humanstudies.pdf) Report produced by the Office of Medical Cannabis at the Minnesota Department of Health. <http://www.health.state.mn.us/topics/cannabis/practitioners/humanstudies.pdf>**

The “Cannabis use and psychotic disorders” section (pages 9-12) provides a brief review of the large literature of studies investigating a potential causal or contributory role of cannabis use in bringing psychotic disorders on or making their outcomes worse. Though study findings regarding use of cannabis among persons with established psychotic disorders are not entirely consistent, most find an association between cannabis use and worse outcomes for at least some of the domains of symptoms. Nearly all the patients in the cited population studies were

using smoked cannabis purchased on the street. The cannabis consumed likely varied in amounts of THC, CBD, and other constituents – but presumably had the typical high levels of THC and low levels of CBD found in street marijuana.

**Schubart CD, Somer IEC, Fusar-Poli P, de Witte L, Kahn RS, Boks MPM. Cannabidiol as a potential treatment for psychosis. *Eur Neuropsychopharm* 2014;24:51-64.**

This article provides a comprehensive review of the categories of evidence for cannabidiol as a potential treatment for psychotic disorders. It includes evidence from: studies of the immune and endocannabinoid systems, animal studies, human experimental studies, imaging studies, epidemiologic studies, and clinical studies. This review concludes, “Evidence from several study domains suggests that CBD has some potential as an antipsychotic treatment. ... Given the high tolerability and superior cost-effectiveness, CBD may prove to be an attractive alternative to current antipsychotic treatment, possibly in specific sub-groups of patients. However, to date the vast majority of the current evidence comes from experimental non-clinical studies and case reports. Although promising, this does not provide evidence that CBD has antipsychotic properties. Therefore, the only clinical evidence currently available for CBD as an antipsychotic agent is the relatively small (n=42) clinical trial published by Leweke et al. (2012). A large double blind randomized clinical trial in a new study population, comparing CBD to an atypical antipsychotic agent is required to truly advance the field. Moreover, illuminating pharmacological pathways through which CBD reduces the experience of psychotic symptoms could also lead to the design of new synthetic agents that act through the endocannabinoid system in ameliorating psychotic symptoms.”

**Iseger TA, Bossong MG. A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research* 2015;162:153-161.**

This systematic review focuses on studies of antipsychotic properties of cannabidiol (CBD) in humans. The paper discusses studies in four categories: the impact of CBD/THC ratios in cannabis on measures relevant for psychosis, 2) Neuropsychological studies with acute CBD administration to healthy volunteers, 3) Neuroimaging studies with acute CBD administration to healthy volunteers, 4) Studies with CBD administration to patients with psychotic symptoms. The paper concludes, “Results show the ability of CBD to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. In addition, CBD may lower the risk for developing psychosis that is related to cannabis use. These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex. The first small-scale clinical studies with CBD treatment of patients with psychotic symptoms further confirm the potential of CBD as an effective, safe and well-tolerated antipsychotic compound, although large randomized clinical trials will be needed before this novel therapy can be introduced into clinical practice.

## National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of schizophrenia were found.

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[Health Canada. Information for Health Care Professionals: Cannabis and the cannabinoids. 2013.](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf) [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/marihuana/med/infoprof-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf)

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Minnesota Department of Health  
Office of Medical Cannabis  
PO Box 64882,  
St. Paul, MN 55164-0882  
651-201-5598  
[Health.Cannabis@state.mn.us](mailto:Health.Cannabis@state.mn.us)  
[www.health.state.mn.us](http://www.health.state.mn.us)



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