Cannabis Use Education

Emerging Evidence for Medical Cannabis

Anxiety Disorders

Summary

Therapeutic potential of cannabinoids for anxiety is inconclusive due to lack of high-quality evidence. Limited evidence suggests that pharmaceutical THC, with or without CBD, may reduce symptoms of anxiety among patients with other medical conditions, particularly multiple sclerosis and chronic pain. CBD also appears to improve self-perception of performance but not anxiety in a simulated public speaking task among patients with social anxiety disorder (SAD). However, serious concerns regarding indirectness, imprecision, and/or inconsistency were identified in all randomized controlled trials (RCTs) evaluated. Overall quality of evidence remains low.

Primary Endpoints

- Remission: diagnostic criteria no longer met
- Change in anxiety symptoms

Secondary Endpoints

- Measures of global functioning: Patient or Caregiver Global Impression of Change (P/CGIC), quality of life, and satisfaction with treatment.
- Incidence of:
  - Adverse events (AEs)
  - Serious AEs (SAEs)
  - Treatment-related AEs
- Incidence of study withdrawals: all-cause, AEs

Findings

17 randomized controlled trials (RCTs) in adult populations (*N*=605) were identified in the clinical literature examining the potential effectiveness of cannabinoids in the treatment of anxiety symptoms. Study designs consisted of 9 parallel and 8 crossover RCTs.

- Seven RCTs used cannabis-naïve participants, for a total proportion of 71.0% of all RCT participants.
- Cannabinoids were primarily studied as adjuvant therapy (12 studies), with a minority of RCTs evaluating cannabinoids as primary treatment (3 studies) or had unclear treatment hierarchies (2 studies).
- Cannabinoid types/formulations studied included nabilone, THC extract, nabiximols, CBD, dronabinol, THC-CBD extract, and Cannabis sativa. Pharmaceutical grade was used in the majority of studies.
- Routes of administration included oral, oral mucosal spray, and smoking.
- Median treatment duration was approximately 4 weeks, ranging from 1–8 weeks.
- Seven RCTs (*n*=252) indicated pharmaceutical THC-CBD significantly reduced symptoms of anxiety compared to placebo (*SMD* -0.25 [95% CI -0.49 to -0.01]) but not compared to an active comparator (400 mg ibuprofen). Treatment effects were investigated in patients with multiple sclerosis, chronic non-cancer pain, Huntington's disease, and Tourette syndrome.
- Two RCTs (*n*=44) examined the effectiveness of pharmaceutical CBD for symptoms of social anxiety disorder (SAD) in a simulated public speaking task. Conditions included healthy control, SAD-placebo, and SAD-CBD groups.

Findings (continued)

- Measures included:
  - Visual Analogue Mood Scale (VAMS) - self-reported state of anxiety
  - Self-Statements during Public Speaking Scale (SPSS) - self-perception of speech performance.
- Among participants with SAD:
  - Although CBD significantly improved mid-speech anxiety compared to placebo, therapeutic effects were transient and were not maintained to study completion and post-test measurements.
  - CBD improved self-perception of speech performance compared to placebo during anticipatory and mid-speech phases.
- Confidence in effect estimates was very low. Quality of evidence was compromised by serious concerns regarding indirectness, imprecision, and inconsistency.
- No RCTs for pharmaceutical THC-CBD included participants with a primary diagnosis of anxiety. Participants reported other diagnoses, primarily multiple sclerosis and chronic non-cancer pain.
- Anxiety disorder was not the primary indication for the cannabinoid in most RCTs, and were typically reported as secondary endpoints for therapeutic investigations of analgesia.
- Risk of bias was considered high in three RCTs and excluded due to incomplete data reporting.
- Although substantial heterogeneity of results was originally reported for THC-CBD trials (I^2=65%), removal of an outlier for treatment duration reduced heterogeneity such that treatment effects remained significant.
- No data on measures of global functioning were reported.

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Depression

Summary

Current evidence recommends against the use of cannabinoids in the treatment of depression. Cannabis use, particularly heavy use, is associated with worsened course of illness and functioning in mood disorders, although strength of evidence is greater for bipolar disorder than major depressive disorder. Concerns regarding indirectness and/or inconsistency were identified in all randomized controlled trials (RCTs) evaluated.

Primary Endpoints

- Remission: diagnostic criteria no longer met
- Change in depressive symptoms

Secondary Endpoints

- Measures of global functioning: Patient or Caregiver Global Impression of Change (P/CGIC), quality of life, and satisfaction with treatment.
- Incidence of:
  - Adverse events (AEs)
  - Serious AEs (SAEs)
  - Treatment-related AEs
- Incidence of study withdrawals: all-cause, AEs

Findings

23 randomized controlled trials (RCTs) in adult populations (*N*=2551) were identified in the clinical literature examining the potential effectiveness of cannabinoids in the reduction of depressive symptoms. Study designs consisted of 10 parallel and 13 crossover RCTs.

- 10 RCTs used cannabis-naïve participants, for a total proportion of 38.5% of all RCT participants.
- Cannabinoids were studied as adjuvant therapy in all RCTs (three cases unclear).
- Cannabinoid types/formulations studied included nabiximols, Cannabis sativa, dronabinol, nabilone, THC extract, and THC-CBD extract. Pharmaceutical grade was administered in the majority of studies.
- Routes of administration included oral, oral mucosal spray, vaporized, and smoking.
- Median treatment duration was approximately 5 weeks, ranging from 3–12 weeks.
- Pharmaceutical THC-CBD (THC or THC-CBD) did not significantly improve depressive symptoms in any RCTs evaluated (*n*=13) compared with either placebo or a single study involving an active comparator (ibuprofen 400 mg).
- No RCTs examined pharmaceutical CBD for depression outcomes.
- One small RCT involving (non-pharmaceutical) medicinal cannabis found no treatment effects of cannabinoids on depression outcomes among participants with chronic non-cancer pain.

Findings (continued)

- Confidence in effect estimates was very low. Quality of evidence was compromised by serious concerns regarding indirectness and inconsistency.
  - No RCTs included participants with a primary diagnosis of depression. Most common primary diagnoses were chronic non-cancer pain and multiple sclerosis.
  - Depression was not the primary indication for the cannabinoid in most RCTs, and were typically reported as secondary endpoints for therapeutic investigations of analgesia and spasticity.
  - Substantial heterogeneity of results in cannabinoid vs. placebo trials was reported (I^2=67%).
- No data on measures of global functioning were reported.

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Glaucoma

Summary

Limited evidence suggests THC may be effective in lowering intraocular pressure (IOP) associated with glaucoma. However, treatment effects are transient (3–4 hours) and do not result in sustained improvement.

The Canadian Ophthalmology Society (COS) and Canadian Glaucoma Society (CGS) issued a **joint policy statement** in October 2018 (Medical Use of Marijuana for Glaucoma). It recommends against the use of cannabinoids due to its short duration of action, incidence of psychotropic and systemic side effects, absence of evidence showing a beneficial effect on disease course, and availability of more effective and less harmful medical, laser, and surgical modalities for the treatment of glaucoma.

Primary Endpoints

- Intraocular pressure (IOP)

Secondary Endpoints

- Visual acuity
- Vital signs
- Psychotropic effects

Findings

- One small randomized controlled trial (RCT) in a small adult sample (*N*=6) examined the effectiveness of THC and CBD on intraocular pressure (IOP).
  - Six patients with ocular hypertension or early primary open angle glaucoma received placebo or one of sublingual:
    - 5 mg THC
    - 20 mg CBD
    - 40 mg CBD
  - IOP was significantly lower than placebo two hours immediately post-administration of THC (23.5 mmHg vs. 27.3 mmHg; *P*=.026), but returned to baseline four hours later.
  - CBD had no therapeutic effect on IOP. Moreover, 40 mg CBD produced a significantly elevated IOP at four hours post-administration (23.2 mmHg to 25.9 mmHg; *P*=.028).
  - No changes in vital signs or visual acuity were reported.
  - One participant experienced acute, transient elevation in anxiety following THC administration.
- Historical evidence has noted THC is effective in lowering IOP through inhalation, intravenous, oral, sublingual and topical routes.
  - However, topical application is not recommended as ocular penetration is poor due to high lipophilicity and low aqueous solubility of cannabinoids. Topical application may also cause local irritability and corneal injury.
  - Treatment effects of THC for IOP are acute with an onset of 1–1.5 hours and do not result in sustained benefit (3–4 hours).

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Insomnia

Summary

Therapeutic potential of cannabinoids for insomnia is inconclusive due to lack of high-quality evidence and conflicting findings across multiple studies and patient populations. Limited evidence suggests THC/CBD have dose-dependent relationships with nocturnal sleep, cognitive performance, and sleepiness, although more recent studies found no changes in sleep architecture or cognition. Cannabinoids may improve sleep-related indicators in chronic pain, fibromyalgia, and obstructive sleep apnea (OSA). Confidence in effect estimates is low due to inconsistency and high likelihood of bias.

Primary Endpoints

- Total sleep time (TST)
- Sleep efficiency
- Sleep onset latency (min)
- REM onset latency (min)
- Wake after sleep onset (min)
- Stage 1, 2, 3, REM sleep (%)
- Lowest, baseline saturation (%)
- Early-morning performance (e.g., memory)
- Additional measures: Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), polysomnography, Maintenance of wakefulness test (MWT), Insomnia Severity Index

Secondary Endpoints

- Respiratory disturbance index (RDI)
- Use of sleeping medication
- Daytime dysfunction
- Apnea-hypopnea index (AHI)
- Pain
- Mood
- Quality of life
- Adverse events (AEs)
- Additional measures: Visual Analog Mood Scale (VAMS), State-Trait Anxiety Inventory (STAI), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Wechsler Adult Intelligence Scale (WAIS) digit symbol substitution and symbol copy tests, Psychomotor Vigilance Test (PVT)

Findings

- A recent crossover RCT observed no significant effects of CBD on the sleep-wake cycle of healthy, cannabis-naïve individuals (*N*=26) via subjective measures and polysomnography.
  - No alterations in sleep architecture were observed.
  - Oral ingestion of CBD oil (300 mg) showed no significant benefit on any primary endpoints (sleep onset latency, REM onset latency, total sleep time, sleep disturbances, REM time, sleep efficiency) over placebo.
  - No significant differences between CBD and placebo groups were found on any cognitive or mood measures (VAMS, STAI, WAIS subtests).
  - Participant exclusion criteria included presence of general medical conditions, psychiatric disorders, or previous history of sleep disorder.
- Dronabinol (10 mg/day; oral capsules) reduced ESS score by −3.8 ± 0.8 points (*P*<.001) compared to placebo (−2.3 ± 1.2 points; *P*=.05) from baseline in adult patients (*N*=73) with moderate to severe obstructive sleep apnea (OSA).
  - Treatment duration of six weeks.
  - No significant effects of dronabinol administration was found for MWT sleep latencies, sleep architecture, and overnight oxygenation parametres.
- An active-control, equivalency crossover RCT (*N*=29) compared the effectiveness of nabilone (0.5–10 mg) to amitriptyline (10–20 mg) in patients with fibromyalgia with chronic insomnia over a two-week period.
  - Nabilone was superior to amitriptyline on both Insomnia Severity Index scores and self-reported restfulness.
  - No treatment effects were found on wakefulness, pain, mood, or quality of life.
  - Most common AEs for nabilone were dizziness, nausea, and dry mouth.
- THC/CBD (oromucosal spray) was found to have variable effects on nocturnal sleep and early-morning behaviour in a non-randomized, double-blind, placebo-controlled trial of young adults (*N*=8). Primary endpoints included nocturnal sleep, early-morning performance, memory, and sleepiness.
  - No effects of 15 mg THC on nocturnal sleep.
  - 15 mg THC resulted in impaired memory, reduced sleep latency, increased sleepiness, and mood changes the next day.
  - Concomitant administration of a 5 mg THC/5 mg CBD formulation up to 15 mg THC/15 mg CBD resulted in decreased stage 3 sleep.
  - 5 mg THC/5 mg CBD increased reaction time on a digit recall task.
  - 15 mg THC/15 mg CBD increased self-reported level of wakefulness.
  - Authors concluded that THC (15 mg) has sedative properties whereas CBD (15 mg) has alerting properties which seemed to counteract residual sedative activity of 15 mg THC the next day.
- One small, double-blind crossover RCT (*N*=10) found no effect of nabilone on sleep quality or quality among patients with post-traumatic stress disorder (PTSD).

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Parkinson's Disease

Summary

Effectiveness of cannabinoids for motor and non-motor symptoms of Parkinson's disease is inconclusive due to lack of high-quality evidence from human trials. Limited evidence suggests nabilone may reduce duration and severity of levodopa-induced dyskinesia (LID), and CBD may improve quality of life and tremor in anxiogenic situations.

Primary Endpoints

- Severity of dyskinesia-resultant disability
- LID
- Motor symptoms
- Quality of life
- Improvement of tremor
- Relevant scales:
  - Unified Parkinson Disease Rating Scale (UPDRS) score
  - Rush Dyskinesia Disability Scale score
  - H&Y: Hoehn & Yahr; LID: (l-dopa)-induced dyskinesias scale score
  - Modified Webster scale
  - Bain scale
  - Tabletarm drawing task
  - Activities of Daily Living (ADL) scale
  - Parkinson's Disease Questionnaire (PDQ-39), 7, on-off
  - Simulated Public Speaking Test (SPST) score
  - Visual Analog Mood Scales (VAMS) score
  - Self-Statements during Public Speaking Scale (SPSS) score
  - Blood pressure
  - Heart rate

Secondary Endpoints

- Sleep quality
- Improvement of anxiety

Findings

Four randomized controlled trials (RCTs) in adult populations (*N*=49) evaluated the effectiveness of cannabinoids on motor and non-motor symptoms of Parkinson's disease.

- Three RCTs found no significant treatment effects of adjuvant cannabinoids on parkinsonian motor symptoms or levodopa-induced dyskinesia (LID).
- Cannabinoid types/formulations studied included nabilone, CBD, and THC.
- One RCT administered rimonabant (selective, inverse agonist for cannabinoid receptor CB1), meclinertant (selective, non-peptide antagonist at NTS1), and osanetant (non-peptide NK3 antagonist).
- Routes of administration included smoking and synthetic oil capsules.
- Nabilone (0.03 mg/kg daily) significantly reduced LID duration and severity during repeated, daily acute levodopa challenges for 14 days in one RCT. However, no changes were observed in the severity of Parkinson's disease symptoms after the challenge.
- A study-specific THC/CBD formulation (ratio 2:1) over four weeks (maximum 0.25 mg/kg daily) did not significantly improve LID, UPDRS motor scores, pain, quality of life, or sleep quality.
- Inverse angonist for CB1 (20 mg/day) over 16 weeks did not improve UPDRS motor scores or UPDRS dyskinesia scores.
- CBD improved quality of life (PDQ-39) and tremor amplitude in anxiogenic situations (SPST) compared to placebo at 300 mg/day.
- CBD improved ADLs and perceptions of stigma compared to placebo at 75 mg/day and 300 mg/day.

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PTSD

Summary

There is insufficient evidence to evaluate the therapeutic potential of cannabinoids for PTSD symptoms. Limited evidence suggests nabilone may improve global functioning and reduce frequency/severity of nightmares associated with PTSD. THC may also modulate threat-related processing in patients with PTSD. Serious concerns regarding inconsistency and imprecision were identified in the clinical literature. Additional randomized controlled trials (RCTs) with larger sample sizes, direct PTSD outcomes, and generalization to more diverse populations are required.

Primary Endpoints

- Mean reduction in CAPS (Clinician-Administered PTSD Scale) Recurring and Distressing Dream Score
- Mean improvement in Clinical Global Impression of Change (CGI-C) score
- Mean improvement on General Well Being Questionnaire (WBQ) score

Secondary Endpoints

- N/A

Findings

Two RCTs in the literature examined the effects of cannabinoids on associated features of PTSD. One small RCT was identified in the literature (*N*=10) examining the effectiveness of pharmaceutical THC-CBD (nabilone) in the treatment of PTSD-associated nightmares. A second RCT (*N*=71) investigated the potential modulation of threat-related processing in individuals with PTSD.

- Participants included 10 military personnel (18–65 years) with PTSD who continued to experience trauma-related nightmares despite standard treatment.
- Inclusion criteria required the traumatic events to be of operational origin and occurred at least two years prior to participation.
- Exclusion criteria included a positive screen for illicit substances, including THC.
- Treatment duration was seven weeks.
- Interventions for which participants had been involved in prior to enrolment (e.g., psychotherapy, medications) were continued for the duration of the study.
- Nabilone capsules were initiated at 0.5 mg, titrated weekly to a maximum of 3 mg based on efficacy (nightmare suppression) and tolerability. Dose at week five was maintained for the final two weeks.
- Measures of nightmare severity included:
  - CAPS Recurrent Distress Dreams Item (Frequency + Intensity)
  - CAPS Difficulty Falling or Staying Asleep Item
  - CGI-C (1=very improved, 7=very much worse)
  - PTSD Dream Rating Scale
  - WBQ (maximum well-being=100)
  - Sleep Diary Log completed by participants during the final week on total sleeptime and number of awakenings per night.

Findings (continued)

- Pre-intervention CGI-C scores were 3.3 ± 0.9 (with a maximum of 4). All participants reported distressing dreams in the past week as baseline.
- Post-intervention scores reflected significant improvement in nightmare frequency.
  - Mean CAPS reduced by −3.6 ± 2.4 (P<.03). CAPS score did not differ significantly pre-intervention (6.3 vs. 6.0), suggested no rebound or carry-over after washout period.
  - Mean CGI-C improved by 1.9 ± 1.1 (P<.05)
  - WBQ improved by 20.8 ± 22.1 (P<.04)
  - Four nabilone participants reported no distressing dreams in the final week.
- No effect on sleep quality or quantity was reported.

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