Cannabis Use Education

Emerging Evidence for Medical Cannabis

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Anxiety Disorders

Summary

Therapeutic potential of cannabinoids for anxiety disorders is inconclusive due to lack of high-quality evidence. Limited evidence suggests pharmaceutical THC-CBD may reduce anxiety symptoms compared to placebo or active comparators. However, serious concerns regarding indirectness, imprecision, and inconsistency were identified in all randomized controlled trials (RCTs) evaluated.

Primary Endpoints

- Remission (diagnostic criteria for anxiety 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 RCTs (n=605) were identified in the clinical literature examining the potential effectiveness of cannabinoids in the treatment of anxiety disorders in adult populations.

- 7 RCTs (n=252) indicated THC-CBD significantly reduced symptoms of anxiety compared to placebo (SMD -0.25 [95% CI -0.49 to -0.01]) but not compared to active comparators (400 mg ibuprofen).
- 2 RCTs (n=44) examined the effectiveness of CBD for social anxiety disorder (SAD). No significant treatment effect was observed between SAD-CBD and SAD-placebo groups.
- 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.
- Median treatment duration was approximately 4 weeks, ranging from 1–8 weeks.
- Cannabinoids were primarily studied as adjuvant therapy.
- Routes of administration included oral, oral mucosal spray, and smoking.
- Confidence in effect estimates was very low. Quality of evidence was compromised by serious concerns regarding indirectness, imprecision, and inconsistency.
  - No RCTs included participants with a primary diagnosis of anxiety. Participants generally reported other diagnoses such as chronic non-cancer pain and multiple sclerosis.
  - Anxiety disorder was not the primary indication for the cannabinoid in most RCTs. Anxiety outcomes were often reported as secondary endpoints.
  - Risk of bias was considered high in 3 RCTs and excluded due to incomplete data reporting.
  - Although substantial heterogeneity of results was originally reported for THC-CBD trials (I2=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.

Anxiety Disorders

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Depression

Summary

No high-quality evidence to support the therapeutic potential of cannabinoids for depressive symptoms. Serious concerns regarding indirectness and inconsistency were identified in all randomized controlled trials (RCTs) evaluated.

Primary Endpoints

- Remission (diagnostic criteria for depression 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 RCTs (n=2551) were identified in the clinical literature examining the potential effectiveness of cannabinoids in the reduction of depressive symptomology in adult populations. No significant treatment effects were found.
  - Cannabinoid types/formulations studied included nabiximols, Cannabis sativa, dronabinol, nabilone, THC extract, and THC-CBD extract. Pharmaceutical grade was used in the majority of studies.
  - No RCTs examined CBD for depression outcomes.
  - Median treatment duration was approximately 5 weeks, ranging from 3–12 weeks.
  - Cannabinoids were primarily studied as adjuvant therapy.
  - Routes of administration included oral, oral mucosal spray, vaporized, and smoking.
- 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. Participants generally reported other diagnoses such as chronic non-cancer pain and multiple sclerosis.
  - Depression was not the primary indication for the cannabinoid in most RCTs. Depression outcomes were often reported as secondary endpoints.
  - Substantial heterogeneity of results in cannabinoid vs. placebo trials was reported (I2=67%).
- No data on measures of global functioning were reported.

Depression

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Drug-Resistant Epilepsy (DRE)

Summary

High-quality evidence is emerging in support of CBD as adjunctive therapy for convulsive and drop seizures in drug-resistant epilepsy (DRE).

Primary Endpoints

- Proportion of patients with ≥50% reduction in convulsive seizure frequency
- Percentage reduction in drop (atonic, tonic, tonic-clonic) seizure frequency
- Percentage reduction in monthly convulsive and total seizures
- Incidence of:
  - Adverse events (AEs)
  - Serious AEs (SAEs)
  - Treatment-related AEs
- Incidence of study withdrawals: all-cause, AEs

Secondary Endpoints

- Percentage reduction in all-type seizure frequency: nondrop, convulsive, nonconvulsive, individual types
- Percentage reduction in convulsive seizure frequency only
- Proportion of patients with convulsive seizure freedom
- Proportion of patients with drop seizure freedom
- Proportion of patients with ≥25%, ≥50%, ≥75% reduction in drop seizure frequency
- Incidence of AEs for:
  - CBD long-term vs. short-term treatment
  - CBD vs. CBN
- Measures of global functioning: Patient or Caregiver Global Impression of Change (P/CGIC), sleep disruption, daytime sleepiness, quality of life, and behavioural adaptation as assessed by validated scales.

Findings

DRE was defined as failure of ≥2 antiepileptic drug (AED) trials to achieve sustained seizure freedom. One RCT widened eligibility criteria to 1–4 AED regimens. The preponderance of evidence investigated the therapeutic potential of CBD, with only a minority of stutides evaluating THC in the context of high-CBD/low-THC ratios.

- CBD was effective in reduction of monthly convulsive seizure frequency in Dravet syndrome (DS).
  - Oral 10–20 mg/kg/day increased proportion of patients with ≥50% reduction in convulsive seizure frequency from baseline when added to existing AED regimens in children and adolescents.
  - One prospective open-label trial reported mean CBD dose of 13.3 mg/kg/day and THC dose of 0.27 mg/kg/day.
  - Treatment effect of CBD was enhanced by concomitant clobazam.
- CBD was effective in reduction of monthly percentage of drop seizure frequency in Lennox-Gastaut syndrome (LGS).
  - Oral 20 mg/kg/day reduced monthly percentage of drop seizure frequency from baseline when added to existing AED regimens in children and adults.
  - Highest proportion of patients achieving ≥25%, ≥50%, ≥75% reductions all occurred in the CBD group vs. placebo.
  - Treatment effects were established early; often within the first 4 weeks of maintenance period and persisted to full treatment duration.

Drug-Resistant Epilepsy (DRE)

Findings (cont.)

- CBD was effective in reduction of monthly percentage of convulsive seizures in TRE of non-DS/LGS etiology.
  - Initiated at 2–10 mg/kg/day (oral), up-titrated to either intolerance or maximum dose of 25–50 mg/kg/day.
  - One observational, longitudinal study reported average CBD dose of 11.4 mg/kg/day with cannabis oil extract (CBD-THC ratio of 20:1).
- Greatest reductions in individual types of seizures occurred for focal, atonic, tonic and tonic-clonic seizures in one open-label intervention trial across 11 epilepsy centres.
  - Initiated at 1–5 mg/kg/day (oral), up-titrated to either intolerance or maximum dose of 25–50 mg/kg/day.
  - Improvement in seizure frequency occurred at all doses and regardless of etiology (DS, LGS, other intractable epilepsies).
- CBD administration was associated with higher rates of AEs in a dose-dependent manner. However, AEs were generally minor, with CBD exhibiting a good safety profile.
  - AEs primarily occurred in the initial 2-week dose escalation/titration period in all treatment groups, and were more common in short-term than long-term treatment.
  - AEs with greatest incidence rates included: somnolence, diarrhea, appetite loss, pyrexia, vomiting, and elevated liver aminotransferase concentrations.
  - Most instances of SAEs were not treatment-related. However, nine cases (6%) of status epilepticus (SE) resulting from treatment was reported in one clinical trial.
- Treatment effect on quality of life (QoL) was highly variable across studies, with some reporting large improvements (>33% in one RCT) in GIC scores and others reporting no significant change following the treatment period.

Drug-Resistant Epilepsy (DRE)

References

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Glaucoma

Summary

Current and historical 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 Opthamology Society (COS) and Canadian Glaucoma Society (CGS) recently issued a joint policy statement on Medical Use of Marijuana for Glaucoma (October 2018). It currently recommends against the use 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 RCT (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 2 hours immediately post-administration of THC (23.5 mmHg vs. 27.3 mmHg; p=.026), and returned to baseline 4 hours later.
  - CBD had no effect on IOP.
  - 40 mg CBD produced a significantly elevated IOP at 4 hours post-administration (23.2 mmHg to 25.9 mmHg; p=.028).
  - No changes in vital signs or visual acuity.
  - One participant experienced acute, transient elevation in anxiety following THC administration.
- Historial evidence has noted THC is effective in lowering IOP through inhalation, intravenous, oral, sublingual and topic routes.
  - 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).

Glaucoma

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Insomnia

Summary

Effectiveness of cannabinoids in the treatment of insomnia is inconclusive due to lack of high-quality evidence. Therapeutic value may be attributed to indirect factors such as analgesia-facilitated sleep improvement among patients with chronic pain.

Primary Endpoints

- Sleep onset latency
- REM onset latency
- Sleep maintenance
- Total sleep time
- Sleep efficiency

Secondary Endpoints

- None reported

Findings

- A recent randomized controlled trial (RCT) observed no significant effects of CBD on the sleep-wake cycle of healthy, cannabis-naïve individuals.
  - Oral ingestion of CBD oil (300 mg) showed no benefit on sleep onset latency, REM onset latency, sleep maintenance, total sleep time, or sleep efficiency over placebo.
  - Participant exclusion criteria included presence of general medical conditions, psychiatric disorders, or previous history of sleep disorder.
- Several studies suggest mood may mediate the relationship between THC consumption and sleep latency and maintenance.

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Parkinson's Disease

Summary

Therapeutic potential of cannabinoids is inconclusive due to lack of high-quality evidence from human trials. Limited evidence suggests nabilone may reduce lelevodopa-induced dyskinesia (LID).

Findings

- 4 randomized controlled trials (n=49) evaluated the effective of CBD, THC-CBD, nabilone, and rimonabant on symptoms of Parkinson's disease.
  - 3 RCTs found no significant treatment effects of adjuvant cannabinoids on parkinsonian motor symptoms or LID.
  - CB-1 receptor antagonists (for CB1 cannabinoid receptors) did not reduce bradykinesia.
  - Treatment effect of cannabinoids or CB-1R antagonists on termor is unclear.
  - 1 RCT reported reduced LID followeing administration of nabilone (CB-1R agonist).

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PTSD

Summary

Insufficient high-quality evidence to evaluate the effectiveness of cannabinoids for symptoms of PTSD. Limited evidence suggests nabilone may improve nightmare severity.

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

- None reported

Findings

- One small randomized controlled trial (RCT) was identified in the literature (n=10) examining the potential effectiveness of nabilone in the treatment of nightmares in the context of post-traumatic stress disorder (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 tablets 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.
- 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 primary endpoints:
- 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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