STEM

Systematically Testing the Evidence on Marijuana

Cannabis for Anxiety and Mood Disorders

Living Systematic Review: Update 1

August 2025

OHSU

Learn More at www.cannabisevidence.org

Table of Contents

Executive Summary 3

Background 5

PICOS 5

Key Questions 6

Methods 6

Findings 7

- GRADE Summary of Findings 9
- Ongoing Studies 24

Discussion 26

Conclusion 26

References 27

Appendix A. Methods 30

- Search Strategy 30
- Detailed Inclusion and Exclusion Criteria 34
- Risk of Bias Assessment 36
- Certainty of Evidence Assessment 36

Appendix B. Full Evidence Tables and Risk of Bias Tables 38

Appendix C. Bibliography of Included Studies 84

Suggested citation: Ayers C, Shaw B, Robalino S, Ward R, Yeddala S, Morasco B, Kansagara D. Cannabis for anxiety and mood disorders. The Systematically Testing the Evidence on Marijuana Project. 2023, updated July 2025. https://www.cannabisevidence.org/evidence-syntheses/anxiety_and_mood_disorders/

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Executive Summary

Background

There are a wide variety of anxiety disorders, and although they differ by the objects or situations that induce anxiety, they share features of excessive anxiety and related behavioral disturbances.[1] Anxiety disorders can interfere with daily activities such as job performance, schoolwork, and relationships.[1]

Depression is a common but serious mood disorder,[2] and like anxiety, there are a wide variety of depressive disorders. It causes severe symptoms that affect how people feel, think, and handle daily activities, such as sleeping, eating, or working.[2]

Bipolar disorder (formerly called manic-depressive illness or manic depression) is a mental illness that causes unusual shifts in a person's mood, energy, activity levels, and concentration. These shifts can make it difficult to carry out day-to-day tasks.[3] There are 3 types of bipolar disorder, and all involve clear changes in mood, energy, and activity levels.[3] These moods range from periods of extremely "up," elated, irritable, or energized behavior (known as manic or hypomanic episodes) to very "down," sad, indifferent, or hopeless periods (known as depressive episodes).[3]

People with anxiety and mood disorders may use cannabis for several reasons, including a lack of effectiveness of standard treatments, the intolerability of side effects associated with standard treatments, and a preference for a natural option.[4]

This is the first update of our previously published review[5] which aims to incorporate new evidence on the effectiveness of cannabis for the treatment of anxiety, depression, and bipolar disorders.

PICOS

Populations

- Adults with a diagnosis of anxiety or mood disorder, as defined in the DSM-5:
  - Anxiety disorders
  - Depressive disorders
  - Bipolar and related disorders

Interventions

- Cannabis preparations, including marijuana, hashish, tincture, hashish oil, infusion, and plant extract or FDA-approved synthesized, pharmaceutically prepared cannabinoids, alone or in combination with other intervention(s).

Comparators

- Any other intervention or a non-exposed control group

GRADE Outcomes

- Anxiety or mood disorder symptoms
- Global improvement and quality of life
- Utilization of health services
- Safety: Adverse events (AEs), serious adverse events (SAEs), and study dropouts to due to AEs

Study Designs

- Controlled clinical trials (CCTs; randomized or non-randomized)
- Observational studies with a comparison group (case-control or cohort studies) that adjust for important confounders

Methods

We searched Ovid MEDLINE ALL, PsycInfo, and EBM CCTR databases, for any CCTs (randomized or non-randomized) or observational studies with a comparison group that adjust for important confounders analyzing cannabis use for anxiety or mood disorders. Laboratory-based studies were excluded. Additionally, studies were required to be in human participants and published in English. We only included studies with a minimum follow-up of 4 weeks, to focus on the use of cannabis for ongoing symptom management rather than acute treatment only. Searches for interventions were conducted in January 2023 and updated May 2, 2025 to capture relevant published studies and were not limited by date. We also searched ClinicalTrials.gov for ongoing studies of cannabis for anxiety or mood disorders.

Two independent researchers conducted risk-of-bias (RoB) assessments; conflicts were handled through discussion, and any disagreements were resolved by a third independent senior researcher. We performed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach on select outcomes: symptom control, quality of life, health care utilization, and safety. Two independent researchers assigned certainty-of-evidence (CoE) ratings from *very low* to *high*; and any disagreements were handled through discussion. A full description of our methods can be found in Appendix A.

Key Findings

Our updated searches returned a total of 808 records after deduplication. We also checked the reference lists of relevant systematic reviews. After screening titles and abstracts, we reviewed 45 full-text articles to determine eligibility.

In total, 2 new randomized controlled trials (RCTs) and 1 quasi-experimental study met the inclusion criteria for the updated review.[35-37] Results of these studies were combined with the 11 studies (in 16

publications) identified by the original review.[6-21] Of the 14 included studies, 5 were in people with an anxiety disorders,[6-8,35,37] 1 was in people with a depressive disorder,[10] and 8 were in people with bipolar disorder.[11-17,36] We also identified 6 ongoing studies on this topic.[38-43]

Anxiety Disorders

CBD

- Use of CBD may be associated with improvements in anxiety, depression, and other anxiety-related symptoms from 3 RCTs,[7,8,35] and 1 quasi-experimental study[37] (total N = 659; Low CoE).
- It is unclear whether CBD impacts functioning (1 RCT[35]; N = 178) or safety (2 RCTs[7,35]; N = 258; Very low CoE).
- No evidence for health care utilization.

THC

- It is unclear whether THC impacts anxiety symptoms (1 CCT[6], and 1 quasi-experimental study[37]; N = 381), or safety (1 CCT[6]; N = 20; Very low CoE).
- No evidence for quality of life and functioning, or health care utilization.

Depressive disorders

Cannabis use (THC vs CBD not assessed)

- It is unclear from the available evidence whether cannabis use impacts depression symptoms, QoL or functioning, or healthcare utilization from 1 NRS[10] (N = 2,577; Very low CoE).
- No evidence for safety.

Bipolar disorders

CBD

- It is unclear whether CBD impacts depression symptom control and safety in patients with bipolar disorder from 1 RCT (N = 35; Very low CoE).[36]
- No evidence for quality of life and functioning, or health care utilization.

Cannabis use (THC vs CBD not specified)

- There is consistent evidence that cannabis use may be associated with increased risk of mania and other bipolar-related symptoms, as well as poorer disease outcomes, such as recovery and remission from 7 NRS[11-17] (N = 4,118; Low CoE).
- It is unclear whether cannabis use impacts quality of life and functioning, or health care utilization from single NRSs (N=3,459 and N=144 respectively; Very low CoE).
- No evidence for safety.

Conclusions

Based on the evidence reviewed, we are not able to determine if cannabis is effective for the treatment of anxiety, depression, or other mood disorders. However, evidence does suggest that CBD may improve symptoms in those with anxiety, while people with bipolar disorder who use cannabis may experience poorer outcomes overall (including increased risk of mania and lower rates of recovery and remission). More research is needed to fully understand the association between cannabis use and health outcomes (including recovery and remission, quality of life, and adverse events) for people with anxiety, depression, or other mood disorders.

Background

There are a wide variety of anxiety disorders and although they differ by the objects or situations that induce anxiety, they share features of excessive anxiety and related behavioral disturbances.[1] Anxiety disorders can interfere with daily activities such as job performance, schoolwork, and relationships.[1] According to the National Center for Health Statistics, National Health Interview Survey (NHIS), in 2022:

- 11.4%, 3.9%, and 2.8% of adults in the US experienced mild, moderate, or severe symptoms of anxiety in the past 2 weeks.[23]
- The percentage of adults who experienced anxiety was highest among those aged 18 to 29 and decreased with age. Women were more likely to experience anxiety than men.[23]
- Non-Hispanic Asian adults were least likely to experience moderate to severe anxiety compared with Hispanic, non-Hispanic white, and non-Hispanic black adults.[23]

Depression is a common but serious mood disorder,[2] and like anxiety, there are a wide variety of depressive disorders. It can cause severe symptoms that affect how people feel, think, and handle daily activities, such as sleeping, eating, or working.[2] According to the 2021 National Survey on Drug Use and Health:[24]

- Among US adults aged 18 or older, 8.3% (or 21.0 million people) had a past-year major depressive episode (MDE) and 5.7% (or 14.5 million people) had an MDE with severe impairment.
- MDEs were highest among young adults aged 18 to 25 (18.6% or 6.2 million people).
- Multiracial adults were more likely to have had an MDE, with Black or Asian adults less likely to have had an MDE than those from other racial or ethnic groups.

Bipolar disorder (formerly called manic-depressive illness or manic depression) is a mental illness that causes unusual shifts in a person's mood, energy, activity levels, and concentration. These shifts can make it difficult to carry out day-to-day tasks.[3] There are 3 types of bipolar disorder and all involve clear changes in mood, energy, and activity levels.[3] These moods range from periods of extremely "up," elated, irritable, or energized behavior (known as manic episodes) to very "down," sad, indifferent, or hopeless periods (known as depressive episodes).[3] Using data from 2001 to 2003, the National Institute of Mental Health estimates:[3]

- Around 2.8% of adults in the US had bipolar disorder in the past year.
- Past-year prevalence of bipolar disorder among adults is similar for males (2.9%) and females (2.8%).
- Around 4.4% of adults will experience bipolar disorder at some time in their lives.

Many people believe that cannabis is beneficial for people with anxiety or depression. This is reflected by the number of people, including Veterans, who report using cannabis for these conditions.[25-28] People with anxiety or mood disorders may use cannabis for several reasons, including a lack of effectiveness of standard treatments, the intolerability of side effects associated with standard treatments, and a preference for a natural option.[4]

This review aims to examine the evidence on the effectiveness of cannabis in the treatment of anxiety, depression, and bipolar disorders.

PICOS

Populations

- Adults with a diagnosis of anxiety or mood disorder, as defined in the DSM-5:
- Anxiety disorders
  - Generalized anxiety disorder (GAD)
  - Social anxiety disorder
  - Panic disorder
  - Agoraphobia
  - Substance/medication-induced anxiety disorder
  - Specific phobia
  - Separation anxiety disorder
  - Selective mutism
  - Anxiety disorder due to another medical condition
  - Other specified anxiety disorder
  - Unspecified anxiety disorder
- Bipolar and related disorders
  - Bipolar I disorder
  - Bipolar II disorder
  - Cyclothymic disorder
  - Substance/medication-induced bipolar and related disorder
  - Bipolar and related disorder due to another medical condition

    - Other specified bipolar and related disorder
    - Unspecified bipolar and related disorder
- Depressive disorders
    - Disruptive mood dysregulation disorder
    - Major depressive disorder, single and recurrent episodes
    - Persistent depressive disorder (dysthymia)
    - Premenstrual dysphoric disorder
    - Substance/medication-induced depressive disorder
    - Depressive disorder due to another medical condition
    - Other specified depressive disorder
        - Unspecified depressive disorder

Interventions

- Cannabis preparations, including marijuana, hashish, tincture, hashish oil, infusion, and plant extract, including Epidiolex (an FDA-approved medication containing cannabidiol) and nabiximols (a nonsynthetic pharmaceutical product with a standard composition and dosage, brand-name Sativex), or FDA-approved synthesized, pharmaceutically prepared cannabinoids Dronabinol (brand-names Marinol and Syndros) and Nabilone (brand-name Cesamet), alone or in combination with other interventions.

Comparators

- Any other intervention or a non-exposed control group

Outcomes

- Anxiety or mood disorder symptoms using validated tools such as:
    - Beck Anxiety Inventory
    - Young Mania Rating Scale
    - Hamilton Depression Rating Scale (HAM-D)
- Relapse and remission of anxiety or mood disorders
- Global improvement, using validated tools such as:
    - Clinical Global Impression of Change
- Use of other medications for anxiety or mood disorders
- Quality of life, using validated tools such as:
    - EQ-5D
- Social functioning (e.g., ability to work)
- Sleep quality, using validated tools such as:
    - Pittsburgh Sleep Quality Index
- Utilization of health services
- Adverse events (AEs) and serious adverse events (SAEs)
- Study dropout due to AEs

Study Designs

- CCTs (randomized or non-randomized)
- Observational studies with a comparison group (case control or cohort studies) that adjust for important confounders

Key Questions

KQ1. What are the effects of cannabis on health outcomes and healthcare utilization for adults with anxiety or mood disorder?

a. Do the effects differ by participant characteristic, such as age or presence of comorbidities?

Methods

For the update, we ran a literature search using Ovid MEDLINE ALL, the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycInfo, for any CCTs (randomized or non-randomized) or observational studies with a comparison group that adjust for important confounders analyzing cannabis for anxiety or mood disorders. We also audited the reference lists of pertinent systematic reviews for potentially relevant publications. Updated searches were conducted in early May 2025 to capture relevant studies published since the previous review search in January 2023. We also searched ClinicalTrials.gov for ongoing studies of cannabis for anxiety or mood disorders (Full search strategies are in Appendix A).

Additional eligibility criteria were studies on human participants, publication in English, and studies conducted outside of a laboratory setting. We only included studies with a minimum follow-up of 4 weeks, to focus on the use of cannabis for ongoing symptom management, rather than acute treatment only.

Two independent researchers conducted risk-of-bias (RoB) assessments using standard instruments adapted from those used by national and international organizations,[29-32] and any disagreements were resolved through discussion. We performed the GRADE approach[33,34] on select outcomes: symptom control, quality of life, health

care utilization, and safety. Two independent researchers assigned certainty-of-evidence (CoE) ratings from *very low* to *high*; with conflicts handled through discussion. We were unable to perform a meta-analysis due to variation in outcome measures and measures of effects across studies, so we qualitatively summarized the findings. For this update, we had enough new data to modify our summary of evidence to summarize the relationship between cannabis exposure and outcome according to the specific cannabinoids where available: THC or CBD predominant formulations (plant-derived or synthesized), whereas previously we had combined all cannabinoids due to the small number of studies that specified cannabinoid compounds in the exposed populations. This aligns with the clinically distinct potential impacts of these compounds. Studies that reported both THC and CBD groups were included in the summary for both interventions. A full description of our methods can be found in Appendix A.

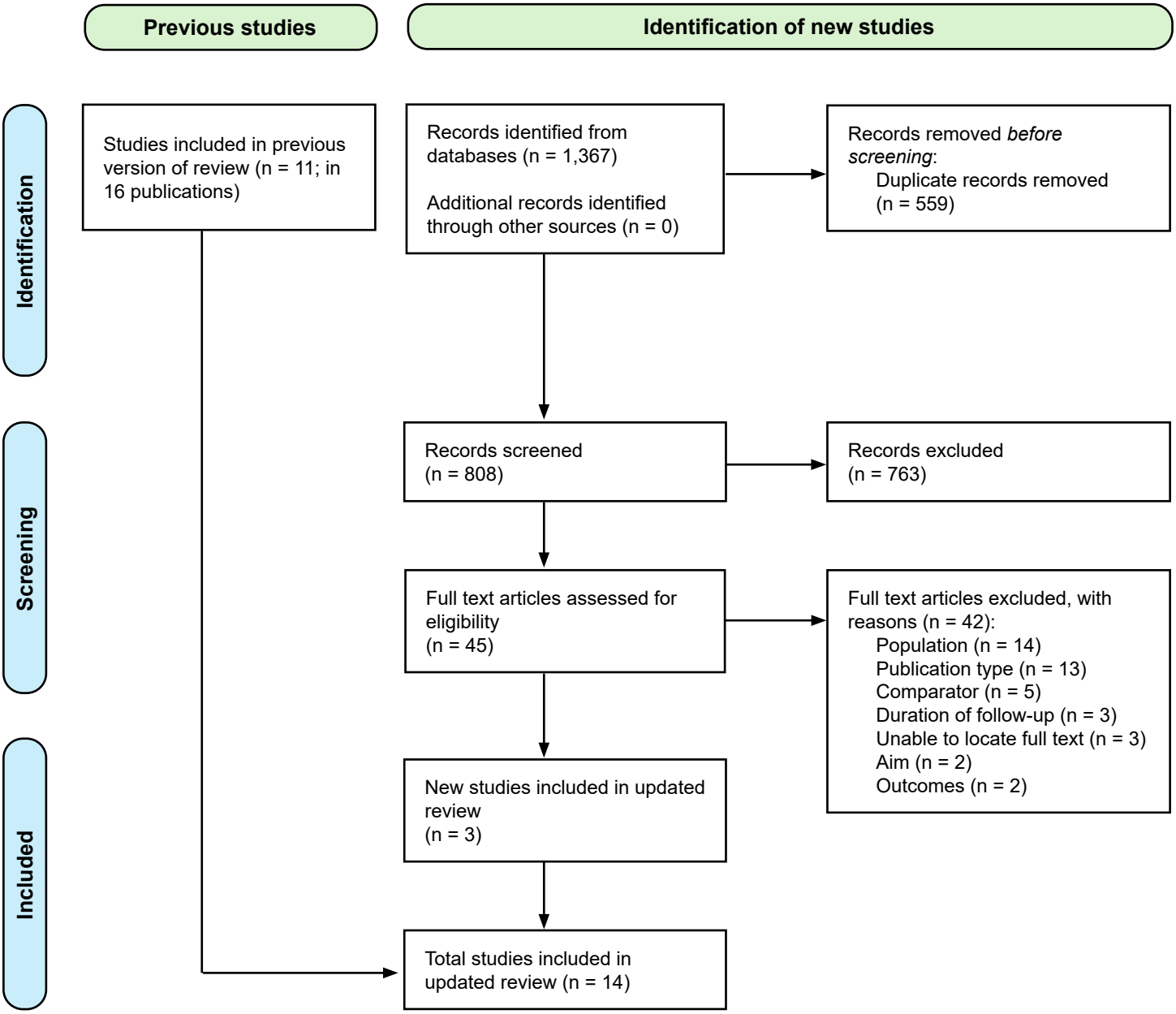
Findings

Our updated searches from February 2023 to May 2025 returned a total of 1,367 records. We also checked the reference lists of relevant systematic reviews but found no additional studies beyond those identified through electronic databases. After duplicate records were removed, 808 records remained (Figure 1). Of these, we assessed the full text of 45 articles to determine eligibility.

In total, 2 new RCTs and 1 quasi-experimental study met the inclusion criteria for the updated review.[35-37] Results of these studies were combined with the 11 studies (in 16 publications) identified by the original review.[6-21]

Of the 14 included studies, 5 were in people with an anxiety disorder,[6-8,35,37] 1 was in people with a depressive disorder,[10] and 8 were in people with bipolar disorder.[11-17,36] An updated summary of our findings and CoE determinations are in Table 1. Study details are in Tables 2 to 4.

Figure 1. Study Flow (2020 PRISMA diagram for updated systematic reviews)



GRADE Summary of Findings

Table 1. Summary of Findings (GRADE)

Outcome Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Anxiety disorders			
Exposure: CBD (low or no THC)			
Symptom control 3 RCTs[7,8,35], and 1 quasi-experimental study[37] N = 659	●●○○ Low	Use of CBD was associated with improvements in anxiety, depression, and other anxiety-related symptoms	Downgraded 1 level each for RoB and indirectness (i.e., limited populations)
Quality of life and functioning 1 RCT[35] N = 178	●○○○ Very low	CBD use was associated with improved functioning compared to placebo	Downgraded 1 level each for RoB, imprecision (i.e., small sample sizes or not assessable), and indirectness (i.e., limited populations)
Health care utilization	No evidence		
Safety 2 RCTs[7,35] N = 258	●○○○ Very low	No association between the use of CBD and AEs	Downgraded 1 level each for RoB, inconsistency (i.e., mixed results) and indirectness (i.e., limited populations)
Exposure: THC (from whole plant or synthesized [e.g. nabilone], with or without CBD)			
Symptom control 1 CCT[6], and 1 quasi-experimental study[37] N = 381	●○○○ Very low	Mixed findings for use of THC and anxiety symptoms	Downgraded 1 level each for RoB, inconsistency (i.e., mixed results) and indirectness (i.e., limited populations)
Quality of life and functioning	No evidence		
Health care utilization	No evidence		
Safety 1 CCT[6] N = 20	●○○○ Very low	No association between the use of nabilone and AEs	Downgraded 1 level each for RoB, imprecision (i.e., small sample sizes or not assessable), and indirectness (i.e., limited populations)
Depressive disorders			
Exposure: Cannabis use (THC vs CBD not assessed)			
Symptom control 1 NRS[10] N = 2,577	●○○○ Very low	No association between cannabis use and remission from MDD Higher levels of cannabis use (i.e., CUD) were associated with significantly higher levels of depression	Downgraded 1 level for indirectness (i.e., NRS with a population using cannabis, but not clear if using for depression specifically)[a]
Quality of life and functioning 1 NRS[10] N = 2,577	●○○○ Very low	No associations between cannabis use and suicidality, functionality, and quality of life in people with MDD	Downgraded 1 level for indirectness (i.e., NRS with a population using cannabis, but not clear if using for depression specifically)[a]

Outcome Number of Studies Sample Size	CoE	Relationship	Rationale for CoE Rating
Health care utilization 1 NRS[10] N = 2,577	●○○○ Very low	No association between cannabis use and health care utilization	Downgraded 1 level for indirectness (i.e., NRS with a population using cannabis, but not clear if using for depression specifically)[a]
Safety	No evidence		
Bipolar disorders			
Exposure: CBD			
Symptom control 1 RCT[36] N = 35	●○○○ Very low	No difference between CBD and placebo for depression, response or remission rates, or mania.	Downgraded 1 level each for RoB, imprecision (i.e., small sample size), and indirectness (i.e., limited population)
Quality of life and functioning	No evidence		
Health care utilization	No evidence		
Safety 1 RCT[36] N = 35	●○○○ Very low	No difference between CBD and placebo for AEs	Downgraded 1 level each for RoB, imprecision (i.e., small sample size), and indirectness (i.e., limited population)
Exposure: Cannabis use (THC vs CBD not specified)			
Symptom control 7 NRS[11-17] N = 4,118	●●○○ Low	Use of cannabis may be associated with increased levels of mania and recurrence and lower rates of recovery and remission	Not downgraded; even though people may not be using cannabis specifically for bipolar disorder, the findings are consistent across the included studies, so we did not downgrade for indirectness in this instance
Quality of life and functioning 1 NRS[17] N = 3,459	●○○○ Very low	Cannabis use was associated with less satisfaction with life and a lower probability of having a relationship compared with no cannabis use Cannabis use was also associated with greater work impairment and being more likely to live apart from a partner	Downgraded 1 level each for RoB and indirectness (i.e., NRS with a population using cannabis, but not clear if using for bipolar disorder specifically)[a]
Health care utilization 1 NRS[16] N = 144	●○○○ Very low	People with bipolar disorder and CUD were more likely to be prescribed conventional antipsychotics than people with bipolar disorder without CUD	Downgraded 1 level each for RoB and for indirectness (i.e., NRS with a population using cannabis, but not clear if using for bipolar disorder specifically)[a]
Safety	No evidence		

Note. [a] *Inconsistency not assessed; single study only. For methods and interpretation of GRADE ratings, see Appendix A. Abbreviations. AE: adverse event; CBD: cannabidiol; CCT: controlled clinical trial; CoE: certainty of evidence; CUD: cannabis use disorder; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; MDD: major depressive disorder; NRS: nonrandomized study; RCT: randomized controlled trial; RoB: risk of bias.*

Anxiety Disorders

In the original report we identified 3 trials (2 RCTs and 1 CCT) evaluating the use of cannabis for anxiety disorders. Since the original report was published, we identified 2 new studies assessing cannabis for anxiety disorders: 1 RCT,[35] and 1 quasi-experimental study (Table 2).[37]

Newly added:

- **CBD:** A 15-week, multi-site RCT conducted by Gundugurti and colleagues in India evaluated the efficacy of cannabidiol (CBD) nanodispersible oral solution versus placebo for mild to moderate anxiety disorders. There were 12 weeks of treatment including titration and tapering. The primary outcome was anxiety as measured by the Generalized Anxiety Disorder 7-item scale (GAD-7) and the Hamilton Anxiety Rating Scale (HAM-A). People randomized to CBD improved over time, while those in the placebo group did not. The CBD group had significantly improved anxiety symptoms compared to the placebo group at the end of treatment as measured by both scales.[35] There were no serious adverse events in either group, but overall, more AEs in the CBD group. We assessed the study as being moderate RoB due to lack of reporting on randomization procedures or allocation concealment and industry funding and affiliation giving the impression of potential author conflicts of interest.
- **THC and CBD:** The quasi-experimental study conducted by Bidwell and colleagues evaluated the effects of commercially available cannabis products (9-tetrahydrocannabinol [THC] and cannabidiol [CBD]) on anxiety symptoms over 4 weeks.[37] All study participants had mild anxiety.[37] The study arms comprised the use of cannabis, specifically THC-dominant, balanced CBD and THC, or CBD-dominant cannabis flower use, and no cannabis use.[37] We assessed this study as being at high risk of bias (RoB) due to an imbalance in participant characteristics between groups, a small sample size, and the potential for off-protocol cannabis use.

Previously included:

- **CBD:** Kwee and colleagues[7] conducted an RCT to determine whether augmentation of exposure therapy with 300 mg of oral CBD per treatment session for 8 weekly sessions would lead to improved anxiety symptoms when compared with placebo (lactose).[7] The RCT included 80 adults diagnosed with social anxiety disorder or panic disorder with agoraphobia, according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria.[7] We assessed this RCT as moderate RoB because of high and differential loss to follow-up.
- **CBD:** Masataka et al.[8] assessed the efficacy of 300 mg CBD daily or placebo (olive oil) for 4 weeks.[8] The RCT included 40 young adults diagnosed with social anxiety disorder, according to DSM-IV and AXIS II Personality Disorder criteria.[8] We assessed this RCT as high RoB, because of limited reporting of randomization, the method of analysis, and uncertainty around baseline differences between groups.
- **Nabilone:** Fabre and colleagues[6] evaluated the effectiveness of nabilone (1 mg 3 times a day) compared with placebo for 28 days in 20 adults with anxiety; no details on how the diagnosis was made were reported, other than noting all participants had psychoneurotic anxiety.[6] We assessed this CCT as high RoB, because of differences in dropout rates between groups, a lack of reporting of allocation, and limited reporting on participant characteristics.

Overall, based on the 3 eligible studies, we found that the use of CBD-predominant cannabis preparations for anxiety was associated with:

- Improvement in symptoms associated with anxiety, including depression (low CoE based on 3 RCTs and 1 quasi-experimental study)[7,8,35,37]
  - No difference in AEs, when compared with placebo (very low CoE, based on 2 RCTs)[7,35]
- None of the eligible studies reported on health care utilization.

Based on 2 eligible studies, it is unclear whether THC has any association with anxiety symptoms (very low CoE; based on 1 CCT[6] and 1 quasi-experimental study[37]). There were no differences in AEs in the 1 CCT of nabilone,[6] and quality of life and healthcare utilization were not evaluated in either study.

Table 2. Summary Study Characteristics and Results in Anxiety Disorders

Citation Setting Country Multi-site or Single-site	Study Design RoB Study Duration	Population	Cannabis Use Comparator	Summary Results
Gundugurti et al., 2025[35] Outpatient India Multi-site	RCT Moderate RoB 15 weeks	178 adults with mild to moderate ICD-11 GAD	CBD (150-300mg/mL bid) nanodispersible oral solution (n = 89) Matched placebo (n = 89)	From baseline to end of treatment, participants receiving CBD experienced greater improvement in anxiety, depression, sleep quality, and global functioning and improvement compared to placebo.
Bidwell et al., 2024[37] Participants recruited from the community US Single-site	Quasi-experimental study High RoB 4 weeks	361 adults with mild anxiety (≥ 5 on GAD-7 scale)	3 cannabis flower product groups: THC-dominant; 1:1 THC:CBD; and CBD-dominant Non cannabis users	All participants experienced significant improvements in anxiety over the study period. Participants who used CBD-dominant cannabis experienced the largest reductions in anxiety over a 4-week period, compared to those who used THC-dominant cannabis.
Kwee et al., 2022[7,9] Mental health care centers The Netherlands Multi-site	RCT Moderate RoB 8 weekly treatment sessions, with follow-up at 6 months	80 adults with social anxiety disorder or panic disorder with agoraphobia	300 mg CBD (powder, purity of greater than 99.9%) per dose per treatment session Placebo (lactose)	CBD does not appear to be associated with reduced anxiety in people undergoing exposure therapy for social anxiety disorder or panic disorder with agoraphobia
Masataka, 2019[8] Hospitals in the Osaka prefecture Japan Multi-site	RCT High RoB Treatment for 4 weeks	40 young adults with social anxiety disorder	300 mg CBD (RSHO-X hemp oil, HempMeds USA) daily Olive oil	CBD may be associated with significant reductions in anxiety and related symptoms and may be associated with an increase in participants wishing to receive further treatment (medication or cognitive behavioral therapy)
Fabre et al., 1978[6] Psychiatric clinic US Single site	CCT High RoB Treatment for 4 weeks	20 adults with anxiety	Nabilone (1 mg 3 times a day; capsule) daily Placebo	Participants who received nabilone reported improved anxiety and other symptoms when compared with placebo Participants who received nabilone also reported greater overall improvement than those who received placebo

Indicates study added since previous version

Abbreviations. AE: adverse event; CBD: cannabidiol; CCT: controlled clinical trial; RCT: randomized controlled trial; GAD: generalized anxiety disorder; PTSD: posttraumatic stress disorder; RoB: risk of bias; THC: Δ-9-tetrahydrocannabinol

Detailed Findings by Study

Based on the moderate-RoB RCT, adults with mild to moderate generalized anxiety disorder (GAD) experienced improvement in symptoms from baseline to end of treatment with CBD compared to placebo.[35] Participants in both groups experienced AEs, with about twice as many in the CBD group. There were no serious AEs.[35]

- Participants receiving CBD had significantly greater improvement in anxiety scores on all three scales:
  - GAD-7: -7.02 (S.E: 0.25, 95% CI -7.52 to -6.52), P < .0001
  - HAM-A: -11.9 (S.E: 0.33, 95% CI -12.6 to -11.3), P < .0001
  - DASS-21: -7.72 (S.E: 0.28, 95% CI -8.27 to -7.17), P < .0001[35]
- Participants receiving CBD also had significantly greater improvement in:
  - Depression (PHQ-9: -6.77 [SE: 0.25, 95% CI -7.26 to -6.28], P < .0001)
  - Sleep quality (PSQI: -6.08 [SE: 0.21, 95% CI -6.50 to -5.66], P < .0001), and
  - Global functioning and improvement (CGI-I: -2.31 [S.E: 0.07, 95% CI -2.44 to -2.18], P < .0001; CGI-S: -1.91 [SE: 0.08, 95% CI -2.06 to -1.75], P < .0001).[35]
- Participants in the CBD group reported more AEs than the placebo group (32% vs. 15%; P = nr). AEs included gastrointestinal symptoms including nausea and upper abdominal pain, general pain or pyrexia, dizziness and headache, and almost all were mild.[35]

In the quasi-experimental study rated as high-RoB comparing high-THC, balanced THC:CBD, high-CBD cannabis, and non-use of cannabis, participants in all groups experienced significant improvements in anxiety over the study period.[37] All participants had mild generalized anxiety at baseline.

- While the cannabis use groups did not significantly differ from one another in anxiety improvement based on the PGIC, they had significantly greater improvement than the non-use group (η^2=0.11, 95% CI [0.05 to 0.18]).[37]
- Participants who used CBD-dominant cannabis experienced the largest reductions in anxiety according to the DASS subscale over a 4-week period, compared to those who used THC-dominant cannabis (difference: −1.03, SE=0.45, *P* = .02; no other significant group differences). [37]

Based on the moderate-RoB RCT, CBD does not appear to be associated with reduced anxiety in people undergoing exposure therapy for social anxiety disorder or panic disorder with agoraphobia.[7] Participants in both groups experienced AEs.[7]

- Participants receiving CBD or placebo had similar levels of anxiety, depression, and fear avoidance at up to 6 months follow-up.[7]
- Measures of overall improvement, medication use, quality of life, and resource use were not reported.[7]
- Participants in both the CBD and placebo groups reported similar numbers of AEs (4 events vs. 6 events; *P* = .40).[7] Isolated AEs included dizziness and drowsiness in the CBD group and sweating, hot flushes, nausea, blurred vision, a bad taste in the mouth, flu and gout attacks, and suicidal thoughts in the placebo group.[7] The participant experiencing suicidal thoughts subsequently withdrew from the trial.[7] Recurrent AEs included tiredness and feeling of a strong blood flow in the CBD group and tiredness, drowsiness, and headaches in the placebo group.[7]

The high-RoB RCT of young adults with social anxiety disorder showed the use of CBD may be associated with significant reductions in anxiety and related symptoms and may be associated with an increase in participants wishing to receive further treatment (medication or cognitive behavioral therapy).[8]

- Participants in the CBD group experienced a significant reduction in anxiety from baseline (measured using the Fear of Negative Evaluation questionnaire [FNE]; a reduction of 5.3 points after 4 weeks; *P* = .02) and participants in the placebo group did not (FNE; a reduction of 0.2 points after 4 weeks; *P* = .29).[8] Participants in the CBD group had significantly lower FNE scores than participants in the placebo group at week 4 (19.1 vs. 23.3; *P* = .002).[8] Similar results were seen when using the Liebowitz Social Anxiety Scale (LSAS).[8]
- Participants in the CBD group were significantly more likely to report wanting further treatment than those in the placebo group (53% vs. 0; *P* < .001).[8]
- Measures of depression or other symptoms, overall improvement, quality of life, resource use and AEs were not reported.[8]

In the high-RoB CCT by Fabre and colleagues,[6] adults with anxiety were assigned to nabilone or placebo. Participants who received nabilone reported improved anxiety and other symptoms when compared with placebo.[6] Participants who received

nabilone also reported greater overall improvement than those who received placebo.[6] Participants in both groups experienced AEs.[6]

- In adults with anxiety, participants in the nabilone group reported significant improvements in anxiety overall ($P < .001$), somatic anxiety ($P < .001$), and psychic anxiety ($P < .001$), as measured by the Hamilton Anxiety Scale [HAS], when compared with participants in the placebo group over 28 days.[6] Participants reported a dramatic improvement by day 3 in the nabilone group.[6]
- Using the 56-item symptom checklist, participants in the nabilone group also reported improvements in depression, somatization, interpersonal sensitivity and efficacy (either statistically significant or approaching significance).[6]
- Nabilone was associated with significant overall improvement when compared with placebo, based on clinician and participant assessment.[6]
- Measures of medication use, quality of life, and resource use were not reported.[6]
- In the nabilone group, the most common AEs were dry mouth, dry eyes, drowsiness, headache, and insomnia. In the placebo group, AEs included mild nausea, muscle weakness, and vascular dilation around the eyes. No participants reportedly withdrew from the study because of AEs, but 5 participants (50.0%) withdrew from the placebo arm due to lack of efficacy.[6]

Depressive Disorders

No studies were identified in the updated search. Previously, we identified 1 NRS assessing the effect of cannabis use on the course of major depressive disorder (MDD). Feingold and colleagues[10] analyzed data from the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Table 3) comparing outcomes for people with MDD, defined as the presence of at least 5 out of 9 symptoms according to DSM-5 criteria, who used cannabis with those who did not.[10] The study included 2,577 people with MDD; of these, 194 had used cannabis between waves 1 and 2 of the NESARC survey (2001 to 2002 and 2003 to 2004). Among those who used cannabis, 121 were diagnosed with comorbid cannabis use disorder (CUD), while 173 did not have CUD. [10] We ultimately assessed this study as moderate RoB because of concerns about under-reporting of cannabis use in NESARC.

Overall, based on the single eligible study, we found:

- No association between cannabis use and remission from MDD; however, higher levels of cannabis use (i.e., CUD) were associated with significantly higher levels of depression (very low CoE, based on 1 NRS)[10]
- No associations between cannabis use and suicidality, functionality, and quality of life in people with MDD (very low CoE, based on 1 NRS)[10]
- No association between cannabis use and health care utilization (very low CoE, based on 1 NRS)[10]

AEs were not reported in the included study.

Table 3. Summary Study Characteristics and Results in Depressive Disorders

Citation Setting Country Multi-site or Single-site	Study Design Risk of Bias	Population	Cannabis Use Comparator	Summary Results
Feingold et al., 2017[10] Population US Multi-site	Prospective, national population survey Moderate risk of bias	2,577 adults with a past-year diagnosis of MDD in Wave 1 who also participated in Wave 2	Cannabis use (any use between Wave 1 and 2 of NESARC) without a diagnosis of CUD Cannabis use (any use between Wave 1 and 2 of NESARC) with a diagnosis of CUD No cannabis use (between Wave 1 and 2 of NESARC)	Associations between cannabis use and a more severe course of MDD do not seem to be attributed to cannabis use itself but to associated sociodemographic and clinical factors

Abbreviations. CUD: cannabis use disorder; MDD: major depressive disorder; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions.

Detailed Findings

In the single eligible study, the course and outcomes for MDD were compared between people who used cannabis, with or without CUD, and people who did not use cannabis, using data from Waves 1 and 2 of NESARC.[10] A high proportion of individuals who met criteria for MDD during the Wave 1 survey no longer met criteria for MDD by Wave 2; rates of remission were similar among those who did and did not use cannabis regardless of CUD status (88.7% cannabis use without CUD vs. 76.8% cannabis use with CUD vs. 82.6% no cannabis use; $P = .19$ for cannabis use without CUD and $P = .08$ for cannabis use with CUD, when compared with no cannabis use).[10]

When compared to people with MDD who did not use cannabis, people with MDD who used cannabis without CUD had no statistically significant differences in:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- 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

When compared to people with MDD who did not use cannabis, people with MDD who used cannabis and had CUD were significantly more likely to experience:

- Depressed mood most of the day, nearly every day (odds ratios [ORs] ranged from 1.50 to 1.77; $P \leq .04$, but were not significant when fully adjusted for baseline suicidality, sociodemographic factors, psychiatric disorders, and substance use disorders)
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (ORs ranged from 2.35 to 2.85; $P \leq .005$ for all models)
- Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day (ORs ranged from 2.30 to 2.87; $P \leq .004$ for all models)
- Insomnia or hypersomnia nearly every day (ORs ranged from 2.30 to 2.62; $P \leq .005$ for all models)
- Psychomotor agitation or retardation nearly every day (ORs ranged from 2.94 to 3.72; $P < .001$ for all models)
- Fatigue or loss of energy nearly every day (ORs ranged from 2.03 to 2.31; $P \leq .02$ for all models)
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (ORs ranged from 2.30 to 2.92; $P \leq .04$ for all models)
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (ORs ranged from 2.09 to 2.29; $P \leq .01$ for all models)
- 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 (ORs ranged from 1.78 to 2.59; $P \leq .003$, but were nonsignificant when fully adjusted for baseline suicidality, sociodemographic factors, psychiatric disorders, and substance use disorders)

After adjusting for baseline confounding factors, no associations were found between cannabis use and suicidality, functionality, and quality of life in people with MDD.[10]

- After controlling for baseline confounders, people with MDD who used cannabis were not significantly more likely to have thought about suicide than people with MDD who did not use.[10]
- After controlling for baseline confounders, people with MDD who used cannabis were not significantly more likely to report being fired from work, having trouble with a boss or coworker, getting divorced or separated, or quitting school more than once at follow-up compared to people with MDD who did not use cannabis.[10]
- No significant differences were found between people with MDD who used cannabis and people with MDD who did not use cannabis in baseline quality of life scores and no significant

association was found between level of cannabis use and quality of life scores at follow-up.[10]

No differences were found in rates of treatment utilization among people with MDD who used cannabis compared to people with MDD who did not use cannabis.[10]

Overall improvement, medication use, and other adverse events (i.e., adverse events not associated with depression) were not reported.[10]

Bipolar Disorders

We identified 1 new RCT[36] in addition to the previous 7 NRSs in 11 publications, evaluating the association between cannabis use and bipolar disorder outcomes (Table 4).[11-21]

Newly added:

- CBD: Pinto and colleagues compared the effects of CBD on depression symptoms in participants with bipolar disorder experiencing major depressive episodes, with an RCT conducted in Brazil over a period of 12 weeks.[36] The primary outcome measure was the change in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline to week 8.[36] We assessed this study as being at moderate RoB due to unclear allocation concealment and blinding implementation, and potential author conflicts of interest.

Previously included:

- Baethge and colleagues[11] explored the sequencing of cannabis use and affective morbidity in 166 people with a first bipolar disorder episode (manic or mixed episode, according to DSM-IV criteria) in a prospective, longitudinal study. We assessed this study as moderate RoB because of the potential for confounding with limited adjustment.
- The EMBLEM study[17,19-21] evaluated the impact of cannabis use on clinical and social outcomes in 3,459 people with bipolar disorder; diagnosis was made according to DSM-IV criteria, International Classification of Diseases criteria (ICD-10), or clinical judgement. We assessed this study as moderate RoB because the study was not designed to assess causality.
- Gruber and colleagues[12] compared the effect of cannabis on mood 4 hours after smoking 3 times a day over a 4-week period in 12 people with bipolar disorder, diagnosed according to DSM-IV criteria.[21] The results were compared with mood scores, again measured 3 times a day over 4 weeks, in 11 people with bipolar disorder who did not use cannabis.[12] We assessed this study as high RoB because of the small sample size and lack of adjustment for confounding.
- Kim and colleagues[13] investigated the impact of regular cannabis use (defined as 3 or more times per week) on the long-term remission (up to 24 months) of mood symptoms in 239 people with bipolar I disorder and schizoaffective disorder, according to DSM-IV criteria. We assessed this study as moderate RoB because of the lack of adjustment for confounding.
- Kvitland and colleagues[14] examined the associations between course of illness in 62 people receiving their first treatment for bipolar I disorder, diagnosed according to DSM-IV criteria, who continued cannabis use over a 12-month period. We assessed this study as moderate RoB because of the small sample size, especially for people who continued to use cannabis.
- Sagar and colleagues[15] assessed the impact of cannabis on mood in 12 people with bipolar disorder who smoked cannabis compared with 18 people with bipolar disorder who did not use cannabis; the diagnoses of bipolar disorder were made according to DSM-IV criteria. Measures of mood were assessed 3 times a day over a 4-week period.[15] We assessed this study as moderate RoB because of the small sample size.
- Strakowski and colleagues[16,18] compared outcomes by cannabis use status in 144 people hospitalized for bipolar 1 disorder, as diagnosed using DSM-IV criteria. The study also compared outcomes for people with bipolar 1 disorder and CUD.[16] We assessed this study as moderate RoB because of loss to follow-up.

Overall, based on the single eligible study examining CBD in bipolar disorder:

- There was no difference between CBD and placebo for depression, response or remission rates, or mania (very low CoE, based on 1 RCT).[36]
- There was no difference in AEs (very low CoE, based on 1 RCT).[36]

For unspecified cannabis use and bipolar disorder, from the 7 eligible NRSs, we found:

- The use of cannabis may be associated with increased levels of mania and recurrent and lower rates of recovery and remission (low CoE, based on 7 NRSs) [11-17]
- Cannabis use was associated with less satisfaction with life and with a lower probability of having a relationship compared with no

cannabis use; use was also associated with greater work impairment and being more likely to live apart from a partner (very low CoE, based on 1 NRS)[17]

- People with bipolar disorder and CUD were more likely to be prescribed conventional antipsychotics than people with bipolar disorder without CUD (very low CoE, based on 1 NRS)[16]
- AEs were not reported in the eligible studies.

Table 4. Summary Study Characteristics and Results in Bipolar Disorders

Citation Setting Country Multi-site or Single-site	Study Design RoB	Population	Cannabis Use Comparator	Summary Results
Pinto et al., 202436 NCT03310593 Single teaching hospital in Brazil	Pilot RCT Moderate RoB 12 weeks	35 participants with bipolar I or II disorder with a current major depressive episode	Cannabidiol (150 to 300 mg/day; n = 19) Matched placebo (n = 16)	• Depression scores declined in both groups over the study period, but there were no statistically significant differences between groups for depression, response, or remission rates, other outcomes (including mania), or AEs.
Baethge et al., 2008[11] Single hospital (international research center) US Single site	Nonrandomized, prospective, longitudinal study Moderate RoB	166 adults admitted for a first manic or mixed episode of type I bipolar disorder	Cannabis use No cannabis use	People with first-episode bipolar I disorder had an increased risk of mania or hypomanic morbidity if they used cannabis in the preceding or same quarter
EMBLEM[17,19-21] Community (inpatient and outpatient units) Europe (14 countries) Multi-site	Nonrandomized, prospective, comparative study Moderate RoB	3,459 adults with bipolar disorder	Current cannabis use (defined as any use) No cannabis use	People with bipolar disorder who also used cannabis exhibited less compliance and higher levels of overall illness severity, mania, and psychosis compared with people with bipolar disorder who did not use cannabis. People with bipolar disorder who also used cannabis were significantly less likely to recover, less likely to experience remission, more likely to experience recurrence, as well as being more likely to have some work impairment and more likely to live apart from a partner
Gruber et al., 2012[12] Community US Multi-site	Nonrandomized, prospective, comparative study (pilot study, with participants selected from a larger ongoing neuroimaging study) High RoB	23 adults with bipolar disorder	Cannabis use – smoking only No cannabis use	People with bipolar disorder who used cannabis reported generally worse mood ratings prior to smoking than people with bipolar disorder who did not use cannabis. After smoking cannabis, people with bipolar disorder reported improvement when compared to people with bipolar disorder who did not use cannabis; however, not all measures of mood were improved with use

Citation Setting Country Multi-site or Single-site	Study Design RoB	Population	Cannabis Use Comparator	Summary Results
Kim et al., 2015[13] Community (public hospitals and private clinics) Australia Multi-site (Melbourne and Geelong)	Nonrandomized, prospective study Moderate RoB	234 adults with bipolar spectrum disorders (bipolar 1 disorder or schizoaffective disorder)	Regular cannabis use (defined as 3 times or more per week) over the past 3 months No cannabis use (defined as less than 3 times per week) over the past 3 months	People with bipolar spectrum disorders who used cannabis regularly (3 times or more per week) had significantly lower rates of remission over a 24-month period than people with bipolar spectrum disorders who did not use cannabis regularly
Kvitland et al., 2015[14] Community (inpatient and outpatient units) Norway Multi-site	Nonrandomized, prospective study Low RoB	62 adults with recent onset bipolar I disorder	Continued cannabis use (defined as any cannabis use in the prior 6 months and use at follow-up) No continued cannabis use (defined as no cannabis use or use only a 1 time point)	People with bipolar I disorder and continued cannabis use (2-3 times per week) compared to people with bipolar I disorder without cannabis use, had increased levels of mania, but similar levels of depression and psychosis
Sagar et al., 2016[15] Not clear US Not clear	Nonrandomized, prospective, comparative study (pilot study, with participants selected from a larger study) Moderate RoB	30 adults with bipolar disorder	Cannabis – smoking only No cannabis use	In general, people with bipolar disorder who used cannabis reported higher levels of depression and higher mania scores prior to smoking cannabis when compared to people with bipolar disorder who did not use cannabis After smoking cannabis, people with bipolar disorder demonstrated improvements in symptoms, resulting in similar levels to those of people with no cannabis use
Strakowski et al., 2007[16,18] Academic medical center US Single site	Nonrandomized, prospective, comparative study Moderate RoB	144 people (aged 12 to 45 years) admitted to hospital for the first time for bipolar I disorder (manic or mixed)	CUD (assessed using the Addiction Severity Index, and meeting DSM-IV criteria for dependence) No CUD	People who developed CUD before bipolar disorder exhibited better recovery than people who developed CUD after bipolar disorder or people who did not use cannabis; however, this association was not significant when mediating variables were included

Indicates study added since previous version

Abbreviations. AE: adverse event; CUD: cannabis use disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; RoB: risk of bias.

Detailed Findings

In the pilot RCT by Pinto and colleagues, participants with bipolar I disorder or bipolar II disorder experiencing a current major depressive episode were randomized to CBD or placebo.[36] Depression scores declined in both groups over the study period, but there were no statistically significant differences between groups for depression, response or remission rates, other outcomes (including mania), or AEs.

- The primary endpoint was MADRS scores at week 8. There was no difference between CBD and placebo (-0.82 [95% CI, -7.81 to 6.17], P = 0.82)[36]
- The secondary efficacy parameters were response rate (defined as a ≥50% reduction from the MADRS baseline score at week 8) and remission rate (defined as MADRS and Young Mania Rating Scale [YMRS] scores ≤7 at week 8) and there was no difference between groups for these outcomes (response rate: CBD 57.9%, Placebo 62.5%, P = 1.0; remission rate: CBD 47.4%, Placebo 31.3%, P = 0.49).[36]
- There was no difference between groups in anxiety (HAM-A Difference: -0.51 (95% CI, -5.55 to 4.54), P = 0.84), functioning (CGI-Severity Difference: 0.52 [95% CI, -0.59 to 1.63], P = 0.36; Functioning Assessment Short Test [FAST] Difference: 0.52 [95% CI, -10.1 to 11.2], P = 0.92), or psychopathology (Brief Psychiatric Rating Scale [BPRS] Difference: -3.24 [95% CI, -7.45 to 0.97], P = 0.13) at week 8.[36]
- Exploratory analysis in 11 people who did not exhibit an early response and subsequently received an increased dose of CBD showed significant improvements in depression from week 2 to week 8 compared with those in the placebo group.[36]

In the longitudinal study by Baethge and colleagues,[11] people with first-episode bipolar I disorder had an increased risk of mania or hypomanic morbidity if they used cannabis in the preceding quarter or in the same quarter. Cannabis use in the preceding quarter was associated with a 11.1% increase in the risk of mania or hypomanic morbidity (95% CI, 5.4% to 16.8%; *P* < .001), and cannabis use in the same quarter was associated with a 11.6% increase in the risk of mania or hypomanic morbidity (95% CI, 5.3% to 17.8%; *P* < .001).[11] However there was no association between mania or hypomanic morbidity and cannabis use in the following quarter, or with depression and cannabis use in any quarter.[11]

Overall, the longitudinal study (EMBLEM), reported in 4 publications,[17,19-21] found that during 12 months of treatment, people with bipolar disorder who also used cannabis exhibited less compliance and higher levels of overall illness severity, mania, and psychosis compared to people with bipolar disorder who did not use cannabis. People with bipolar disorder who also used cannabis were significantly less likely to recover, less likely to experience remission, more likely to experience recurrence, as well as being more likely to have some work impairment and to live apart from a partner.[17,19-21]

- People who currently used cannabis experienced significantly lower levels of recovery (OR, 0.39; 95% CI, 0.21 to 0.73), lower levels of remission (OR, 0.57; 95% CI, 0.37 to 0.89), and higher levels of recurrence (OR, 1.69; 95% CI, 1.11 to 2.58).[21] There was no significant association with relapse.[21]
- No significant association was found between any cannabis use and CGI-BP depression scores at 12 months (1.70 vs. 1.70; *P* ≥ .05).[17]
- People with bipolar disorder who used cannabis had significantly higher CGI-BP mania scores at 12 months than people who did not use cannabis (2.0 vs, 1.9; *P* = .001 over the 12 months).[17]
- People with bipolar disorder who used cannabis had significantly higher CGI-BP hallucination or delusion scores at 12 months than people who did not use cannabis (1.6 vs. 1.4; *P* = .006 over the 12 months).[17]
- There was no significant association between current cannabis use and switching from manic or mixed episodes to depression.[20]
- People with bipolar disorder who used cannabis had significantly higher CGI-BP overall illness scores at 12 months than people who did not use cannabis (2.4 vs. 2.3; *P* = .004 over the 12 months).[17]
- People with bipolar disorder who used cannabis had significantly lower treatment compliance (OR, 1.38; 95% CI, 1.12 to 1.72; *P* = .003); however, when other substance use was included, the relationship was no longer significant.[17]
- People with bipolar disorder who used cannabis were significantly less likely to have a relationship over the 12 months (OR, 1.64; 95% CI, 1.13 to 2.38; *P* = .009).[17] People who currently used cannabis were also significantly more likely to be living apart from a partner (OR, 2.91; 95% CI, 1.37 to 6.17).[21]
    - People with bipolar disorder who used

cannabis were significantly less likely to engage in social activities over the 12 months (5.1% vs. 9.1%; *P* = .02); however, when age, age of onset, and alcohol abuse were included, the relationship was no longer statistically significant.[17]

- People with bipolar disorder who used cannabis were significantly more likely to have some work impairment (OR, 1.85; 95% CI, 1.12 to 3.04).[21]
- People with bipolar disorder who used cannabis were significantly more likely to report being dissatisfied with their life at 12 months (22.4% vs. 14.3%; *P* = .007 over the 12 months).[17]
- There was no significant association between any cannabis use and independent living, the number of dependents to care for and the extent of work impairment over 12 months.[17,21]

Generally, in the study by Gruber and colleagues, people with bipolar disorder who used cannabis reported worse mood ratings prior to smoking than people with bipolar disorder who did not use cannabis. After smoking cannabis, people with bipolar disorder reported improvement on several scales over the 4 weeks when compared to people with bipolar disorder who did not use cannabis; however, not all measures of mood were improved with use.[12] Over the 4 weeks, the study showed that cannabis use in people with bipolar disorder was associated with:[12]

- Significantly lower mean total mood disturbance (TMD) score (12.22 cannabis use vs. 20.60 no cannabis use; *P* =.002)
- Significantly lower mean confusion levels, as measured on the Profile of Mood States (POMS; 4.94 cannabis use vs. 7.41 no cannabis use; *P* < .001)
- Significantly lower mean tension levels, as measured on the POMS (3.70 cannabis use vs. 6.58 no cannabis use; *P* < .001)
- Significantly lower mean fatigue levels, as measured on the POMS (5.30 cannabis use vs. 6.96 no cannabis use; *P* = .005)
- Significantly higher mean depression scores, measured using the MADRS (11.73 cannabis use vs. 6.65 no cannabis use; *P* ≤ .05)
- Significantly higher mean symptoms of mania, measured using the YMRS (5.38 cannabis use vs. 3.70 no cannabis use; *P* ≤ .05)
- No significant differences between groups for anxiety, as measured by the HAM-A, or vigor, anger, and depression, as measured on the POMS

In a similar study from the same organization, Sagar and colleagues[15] found that people with bipolar disorder who used cannabis generally reported higher levels of depression and a tendency for higher mania scores prior to smoking cannabis when compared with people with bipolar disorder who did not use cannabis. After smoking cannabis, people with bipolar disorder demonstrated improvements in symptoms, resulting in similar levels to those of people with no cannabis use.[15]

In the study by Kim and colleagues,[13] people with bipolar spectrum disorders who used cannabis regularly (3 times or more per week) had significantly lower rates of remission over a 24-month period than people with bipolar spectrum disorders who did not use cannabis regularly. In people with bipolar spectrum disorders, regular cannabis use was associated with:[13]

- Significantly lower levels of remission from depression (defined as HAM-D score of ≤ 8; median, 22 cannabis use vs. 33 no cannabis use; *P* = .04)
- Significantly lower levels of total remission (defined as remission of both mania and depression; median, 11 cannabis use vs. 33 no cannabis use; *P* = .03)

However, although the rates of remission from mania alone were lower in the group of people who used cannabis regularly, the difference was not statistically significant (defined as YMRS score of ≤ 12; median, 78 cannabis use vs. 89 no cannabis use; *P* = .051).[13] In subgroup analyses, cannabis use was associated with significantly lower depression and total remission rates in women and participants prescribed mood stabilizers alone. However, in men and participants prescribed olanzapine or a mood stabilizer, cannabis use was associated with significantly lower remission of mania.[13] A post-hoc analysis showed that all remission rates were significantly lower in the concurrent cannabis and the tobacco-smoking group compared to the non-smoker group.[13]

In the study by Kvitland and colleagues,[14] people with bipolar I disorder and continued cannabis use (2 to 3 times per week), compared to people with bipolar I disorder who had discontinued cannabis use or who had never used cannabis, had the following:

- Increased levels of mania, as indicated by significantly higher scores on the YMRS (7.33 continued cannabis use vs. 2.25 no continued cannabis use; *P* = .005)
- Similar levels of depression, as measured

on the Inventory of Depression Scale (IDS; 18.50 continued cannabis use vs. 11.17 no continued cannabis use; *P* = .10) and psychosis, as measured on the Positive and Negative Syndrome Scale-Psychotic (PANSS-P, 9.67 continued cannabis use vs. 8.70 no continued cannabis use; *P* = .38)

After controlling for confounders, the association between elevated mood (i.e., increased levels of mania) at 1 year, as indicated by the YMRS, and continued cannabis use remained significant (*P* = .004).[14]

Continued use of cannabis was also associated with significantly worse global functioning, measured using the Global Assessment Of Functioning scale, at 1 year (49.0 continued cannabis use vs. 66.0 no continued cannabis use; *P* = .013).[14] After controlling for confounders, the association between worse functioning at 1 year, as indicated by the YMRS, and continued cannabis use remained significant (*P* = .004).[14]

Strakowski and colleagues observed that people who developed CUD before bipolar disorder exhibited better recovery than people who developed CUD after bipolar disorder or people who did not use cannabis.[16] Although when adjusted for potential mediator variables these results did not persist.[16]

- People who developed CUD before bipolar disorder were significantly more likely to achieve affective symptom recovery than people who developed bipolar disorder before CUD or who did not have CUD (*P* = .003). There was no significant difference in recovery between people who developed bipolar disorder before CUD and those who did not have CUD (*P* = .76). However, when adjusted for age, sex, education, presence of psychosis, age at bipolar disorder onset, and history of an alcohol or other drug use disorder at the index assessment, the differences in time to recovery were no longer statistically significant (*P* = .33).
- There was no difference between groups for recurrence of affective episodes (*P* = .16), time to recurrence (*P* = .91), percentage of weeks in recovery (*P* = .11), or the numbers of weeks with subdromal affective symptoms (*P* = .62).
- People who developed bipolar disorder before CUD had significantly longer time in an affective episode than people who developed CUD before bipolar disorder, or who did not have CUD (*P* = .004), especially in mixed (*P* = .03) episodes when compared with no CUD.
- Participants in both comorbid groups experienced significantly more rapid cycling than participants without CUD (12% vs. 19% vs. 5%; *P* = .04).
- There was no difference between groups for full adherence with at least 1 mood stabilizer (56% vs. 42% vs. 56%; *P* ≥ .05).
- There was no difference between groups in the use of lithium, anticonvulsants, atypical antipsychotics, or antidepressants; however, there was significantly more use of conventional antipsychotics in the comorbid groups (24% vs. 22% vs. 7%; *P* = .02).

Ongoing Studies

We also identified 6 ongoing RCTs of cannabis in anxiety, depression, or other mood disorders (Table 5).[38-43]

Table 5. Summary Study Characteristics of Ongoing Studies

Study ID Study Design Location	Population Estimated enrollment	Intervention Comparator Duration	Eligible Outcomes	Estimated Completion Date
2024-514783-78-00[38] RCT Netherlands	Dutch military personnel or Veteran, aged 18 to 65, awaiting treatment for PTSD or anxiety disorders N = 82	CBD oil Placebo 3-month follow-up	• Anxiety • Fear extinction and consolidation • Stress regulation • Sleep	December 2025
NCT06672666[41] RCT US	Adults (18-55) with moderate to severe anxiety N = 30	CBD Placebo 4 weeks	• Anxiety symptoms • Sleep disturbance	December 2026
NCT06526208[39] RCT US	Adults (18-45) with ASD and anxiety N = 108	MB-IMP, an oil-based solution containing CBD and THC (23:1), taken orally Placebo (MCT Oil) 8 weeks	• Anxiety symptoms • Socialization • Repetitive behaviors • Aberrant behaviors	September 2027
NCT06290063[40] RCT US	Older adults (60+) who seek to use cannabis for pain, anxiety, or mood problems N = 385	Full-Spectrum Hemp-Derived CBD (200mg CBD/4mg THC) or Broad-Spectrum Hemp-Derived CBD (200mg CBD) Placebo 8 weeks	• Anxiety • Depression • Sleep • Motor function • Balance • Cognition • Pain • Memory • Change in condition • Inhibitory control	August 2028
NCT05867849[43] RCT Canada	Adults, aged 19 to 70, with bipolar disorder N = 360	CBD Placebo 6 weeks	• Depression • Response • Remission • Mania • Anxiety • Global improvement • Sleep • Suicidal thoughts and behaviors • Functioning • Quality of life • Health services utilization • Adverse events	December 2030

NCT04603781[42] RCT US	Adults, aged 18 to 70, with COVID-19-induced stress reactions including 1 or more of the following: anxiety, depression, anger, substance use, or sleep disturbance N = 160	Pure hemp-derived CBD isolate Full spectrum CBD oil Broad- spectrum CBD oil Placebo 6 weeks	• Distress • Depression • Anxiety • Anger • Alcohol use • Sleep • Disability	Originally, December 2023 (trial status "suspended" for lack of IND as of 2023)

Abbreviations. ASD: autism spectrum disorder; CBD: cannabidiol; IND: Investigational New Drug; MCT: medium-chain triglyceride; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; THC: tetrahydrocannabinol.

Discussion

In 2017, a survey of 16,280 US adults found that about 81% of respondents believed cannabis had at least 1 benefit.[25] The most common benefit cited was pain management (66%), followed by treatment of diseases, such as epilepsy and multiple sclerosis (48%), and relief from anxiety, stress, and depression (47%).[25] For this update, we found 3 new studies of cannabis for the treatment of anxiety, depression, or other mood disorders. Based on the updated evidence in this systematic review, we are not able to determine if cannabis is effective for the treatment of any of these conditions.

For almost all conditions, outcomes, and formulations of cannabis, our certainty of evidence was very low. For anxiety, the only outcome for which our certainty was greater than very low was low certainty evidence for a possible association with CBD and improvement in anxiety symptoms, with our certainty downgraded for RoB in the included studies and limited applicability. For THC, the evidence on anxiety symptoms was mixed and the certainty very low. Most of the included studies only reported short periods of cannabis use (around 4 to 8 weeks, with one 12-week study).[6-83537] As we noted previously, further complicating the relationship, anxiety is a common symptom of cannabis withdrawal.[44] People who use cannabis regularly and for longer periods of time may experience withdrawal symptoms on stopping cannabis that they ascribe to anxiety, rather than to withdrawal.

In the single NRS, based on a national survey and looking at the course of MDD and cannabis use, the use of cannabis (for any reason, not specifically for depression or its symptoms) was not associated with worse outcomes.[10]

In people with bipolar disorder, one new trial of CBD versus placebo in those experiencing a major depressive episode found no difference in depression symptoms, response or remission rates, mania, or AEs. [36] The rest of the studies were NRSs which did not specify the cannabis formulations or doses used. However, there was consistent evidence that cannabis use may be associated with an increased risk of mania and other bipolar-related symptoms, as well as poorer disease outcomes, such as recovery and remission (low CoE).[11-17,21]

However, these findings should be viewed with caution. Most studies had clear methodological limitations, leading us to rate them as having moderate to high RoB. The NRSs were not limited to people using cannabis only for their primary diagnosis but included people who were using cannabis for any reason, including non-medical use. The NRSs also did not provide any information on the type or dose of cannabis being used. The evidence was graded as low to very low by outcome, limiting our ability to draw robust conclusions on the effectiveness of cannabis for the treatment of anxiety, depression, or other mood disorders. In addition, studies used a variety of different measures and key outcomes were often not reported, hindering our ability to combine results and highlighting significant gaps in the evidence base.

Even with these limitations, we believe the evidence included in this review does suggest people with bipolar disorder who use cannabis may experience poorer outcomes overall, with consistent findings across the included NRSs.

Many of the published studies often cited in the literature as demonstrating the effectiveness of cannabis for anxiety, depression, or other mood disorders focus only the immediate effect on symptoms and other outcomes, often in a laboratory or simulated setting. For example, the RCT by Bergamaschi and colleagues[22] found that CBD significantly reduced anxiety in people with social anxiety disorder in a simulated public speaking test over a 3-hour period. Our review is focused on the use of cannabis for the chronic treatment of anxiety, depression, or other mood disorders, and hence, studies reporting only on acute response to cannabis were not included because such findings may not translate into sustained and meaningful improvements in the longer term.

Conclusion

In summary, there is a lack of robust evidence supporting the use of cannabis for anxiety, depression, or other mood disorders. However, evidence does suggest that CBD may improve symptoms in those with anxiety, while people with bipolar disorder who use cannabis may experience poorer outcomes overall. More research is needed to fully understand the association between cannabis use and outcomes (including recovery and remission, quality of life, and adverse events) for people with anxiety, depression, or other mood disorders. Ideally, this research would be well-conducted RCTs and cohort studies reporting on symptom control, as well as other patient-important outcomes (such as quality of life and functioning) and AEs.

References

1. National Institute of Mental Health. Any anxiety disorder. https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder. Accessed March 17, 2023.
2. National Institute of Mental Health. Depression. https://www.nimh.nih.gov/health/topics/depression. Accessed March 17, 2023.
3. National Institute of Mental Health. Bipolar disorder. https://www.nimh.nih.gov/health/topics/bipolar-disorder. Accessed March 17, 2023.
4. Garcia-Romeu A, Elmore J, Mayhugh RE, et al. Online survey of medicinal cannabis users: qualitative analysis of patient-level data. Front Pharmacol. 2022;13:965535. doi: 10.3389/fphar.2022.965535.
5. Shaw B, Robalino S, Ayers C, et al. Cannabis for anxiety and mood disorders. The Systematically Testing the Evidence on Marijuana Project. 2023; https://www.cannabisevidence.org/evidence-syntheses/anxiety_and_mood_disorders/.
6. Fabre LF, McLendon DM, Stark P. Nabilone, a cannabinoid, in the treatment of anxiety: an open-label and double-blind study. Current Therapeutic Research. 1978;24(2):161-169.
7. Kwee CM, Baas JM, van der Flier FE, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: a randomised controlled trial. Eur Neuropsychopharmacol. 2022;59:58-67. doi: 10.1016/j.euroneuro.2022.04.003.
8. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. Front Psychol. 2019;10:2466. doi: 10.3389/fpsyg.2019.02466.
9. van der Flier FE, Kwee CMB, Cath DC, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: study protocol of a randomized controlled trial. BMC Psychiatry. 2019;19(1):69. doi: 10.1186/s12888-019-2022-x.
10. Feingold D, Rehm J, Lev-Ran S. Cannabis use and the course and outcome of major depressive disorder: A population based longitudinal study. Psychiatry Res. 2017;251:225-234. doi: 10.1016/j.psychres.2017.02.027.
11. Baethge C, Hennen J, Khalsa HM, Salvatore P, Tohen M, Baldessarini RJ. Sequencing of substance use and affective morbidity in 166 first-episode bipolar I disorder patients. Bipolar Disord. 2008;10(6):738-741. doi: 10.1111/j.1399-5618.2007.00575.x.
12. Gruber SA, Sagar KA, Dahlgren MK, Olson DP, Centorrino F, Lukas SE. Marijuana impacts mood in bipolar disorder: a pilot study. Ment Health Subst Use. 2012;5(3):228-239. doi: 10.1080/17523281.2012.659751.
13. Kim SW, Dodd S, Berk L, et al. Impact of cannabis use on long-term remission in bipolar I and schizoaffective disorder. Psychiatry Investig. 2015;12(3):349-355. doi: 10.4306/pi.2015.12.3.349.
14. Kvitland LR, Melle I, Aminoff SR, et al. Continued cannabis use at one year follow up is associated with elevated mood and lower global functioning in bipolar I disorder. BMC Psychiatry. 2015;15:11. doi: 10.1186/s12888-015-0389-x.
15. Sagar KA, Dahlgren MK, Racine MT, Dreman MW, Olson DP, Gruber SA. Joint effects: a pilot investigation of the impact of bipolar disorder and marijuana use on cognitive function and mood. PLoS ONE. 2016;11(6):e0157060. doi: 10.1371/journal.pone.0157060.
16. Strakowski SM, DelBello MP, Fleck DE, et al. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. Arch Gen Psychiatry. 2007;64(1):57-64. doi: 10.1001/archpsyc.64.1.57.
17. van Rossum I, Boomsma M, Tenback D, Reed C, van Os J, Board EA. Does cannabis use affect treatment outcome in bipolar

disorder? A longitudinal analysis. J Nerv Ment Dis. 2009;197(1):35-40. doi: 10.1097/NMD.0b013e31819292a6.

18. Strakowski SM, DelBello MP, Fleck DE, Arndt S. The impact of substance abuse on the course of bipolar disorder. Biol Psychiatry. 2000;48(6):477-485. doi: 10.1016/s0006-3223(00)00900-8.

19. Haro JM, van Os J, Vieta E, et al. Evidence for three distinct classes of 'typical', 'psychotic' and 'dual' mania: results from the EMBLEM study. Acta Psychiatr Scand. 2006;113(2):112-120. doi: 10.1111/j.1600-0447.2005.00692.x.

20. Vieta E, Angst J, Reed C, Bertsch J, Haro JM, board Ea. Predictors of switching from mania to depression in a large observational study across Europe (EMBLEM). J Affect Disord. 2009;118(1-3):118-123. doi: 10.1016/j.jad.2009.02.007.

21. Zorrilla I, Aguado J, Haro JM, et al. Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? Acta Psychiatr Scand. 2015;131(2):100-110. doi: 10.1111/acps.12366.

22. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology. 2011;36(6):1219-1226. doi: 10.1038/npp.2011.6.

23. Terlizzi E, Zablotsky B. National Health Statistics Reports. Number 213. Symptoms of Anxiety and Depression Among Adults: United States, 2019 and 2022. 2024; https://www.cdc.gov/nchs/data/nhsr/nhsr213.pdf.

24. National Survey on Drug Use and Health. Key substance use and mental health indicators in the United States: results from the 2021 National Survey on Drug Use and Health. 2022; https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021NSDUHFFRRev010323.pdf. Accessed March 17, 2023.

25. Keyhani S, Steigerwald S, Ishida J, et al. Risks and benefits of marijuana use: a national survey of U.S. Adults. Ann Intern Med. 2018;169(5):282-290. doi: 10.7326/M18-0810.

26. Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: systematic review and meta-analysis. Soc Sci Med. 2019;233:181-192. doi: 10.1016/j.socscimed.2019.06.005.

27. McNabb M, Durante KA, Trocchio S, et al. Self-reported medicinal cannabis use as an alternative to prescription and over-the-counter medication use among US military veterans. Clin Ther. 2023;45(6):562-577. doi: 10.1016/j.clinthera.2023.04.003.

28. Dai H, Richter KP. A national survey of marijuana use among US adults with medical conditions, 2016-2017. JAMA Netw Open. 2019;2(9):e1911936. doi: 10.1001/jamanetworkopen.2019.11936.

29. National Heart, Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies. 2018; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed May 30, 2018.

30. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. NICE; 2014; https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf. Accessed December 15, 2015.

31. Scottish Intercollegiate Guidelines Network. Methodology checklist 3: cohort studies. 2012; http://www.sign.ac.uk/checklists-and-notes.html. Accessed May 30, 2018.

32. Scottish Intercollegiate Guidelines Network. Methodology checklist 2: randomised controlled trials. 2015; http://www.sign.ac.uk/checklists-and-notes.html. Accessed May 9, 2017.

33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of

recommendations. Bmj. 2008;336(7650):924-926. doi: 10.1136/bmj.39489.470347.AD.

34. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. 2014; http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed December 15, 2015.

35. Gundugurti PR, Banda N, Yadlapalli SSR, et al. Evaluation of the efficacy, safety, and pharmacokinetics of nanodispersible cannabidiol oral solution (150 mg/mL) versus placebo in mild to moderate anxiety subjects: A double blind multicenter randomized clinical trial. Asian J Psychiatr. 2024;97:104073. doi: 10.1016/j.ajp.2024.104073.

36. Pinto JV, Crippa JAS, Cereser KM, et al. Cannabidiol as an adjunctive treatment for acute bipolar depression: a pilot study: le cannabidiol comme traitement d'appoint de la depression bipolaire aigue : une etude pilote. Can J Psychiatry. 2024;69(4):242-251. doi: 10.1177/07067437231209650.

37. Bidwell LC, Martin-Willett R, Skrzynski C, et al. Acute and extended anxiolytic effects of cannabidiol in cannabis flower: a quasi-experimental ad libitum use study. Cannabis Cannabinoid Res. 2024;22:22. doi: 10.1089/can.2023.0187.

38. EUClinicalTrials.eu. 2024-514783-78-00. BOOSTCAMP: boosting the endocannabinoid system before the treatment of anxiety symptoms. 2024; https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-514783-78-00. Accessed June 17, 2025.

39. ClinicalTrials.gov. NCT06526208. Investigating a Marijuana-based Compound as a Treatment for Anxiety in Autistic Adults. 2024; https://clinicaltrials.gov/study/NCT06526208. Accessed June 17, 2025.

40. ClinicalTrials.gov. NCT06290063. Cannabidiol and Older Adult Cannabis Users (QUARTz). 2024; https://clinicaltrials.gov/study/NCT06290063. Accessed June 17, 2025.

41. ClinicalTrials.gov. NCT06672666. Use of CBD in the Treatment of Anxiety. 2025; https://clinicaltrials.gov/study/NCT06672666. Accessed June 17, 2025.

42. ClinicalTrials.gov. NCT04603781. Use of CBD oil for reducing the negative emotional impact of COVID-19: a randomized placebo-controlled clinical trial. 2020; https://clinicaltrials.gov/ct2/show/NCT04603781. Accessed June 6, 2023.

43. ClinicalTrials.gov. NCT05867849. Cannabidiol adjunctive therapy for acute bipolar depression: a randomized double-blind, placebo controlled trial. 2023; https://clinicaltrials.gov/ct2/show/NCT05867849. Accessed June 6, 2023.

44. Connor JP, Stjepanovic D, Budney AJ, Le Foll B, Hall WD. Clinical management of cannabis withdrawal. Addiction. 2022;117(7):2075-2095. doi: 10.1111/add.15743.

Appendix A. Methods

Search Strategy

We ran a literature search using Ovid MEDLINE ALL, the Cochrane Central Register of Controlled Trials (CENTRAL), and PsycInfo for any controlled clinical trials (randomized or non-randomized) or observational studies with a comparison group that adjust for important confounders analyzing cannabis for anxiety or mood disorders. We also audited the reference lists of pertinent systematic reviews for potentially relevant publications. Searches for interventions were not limited by date, and searches were conducted in May 2025 to capture relevant studies published. We also searched ClinicalTrials.gov for ongoing randomized controlled trials (RCTs) of cannabis for anxiety or mood disorders.

Ovid MEDLINE

Ovid MEDLINE(R) ALL <1946 to May 01, 2025>

1. *Mood Disorders/ or ((Mood or Affective) adj2 Disorder*).ti,ab,kf,ot. 50014
2. *Anxiety Disorders/ or *Anxiety, Separation/ or ((Persistent or Disabling or disorder* or neuros* or neurotic or treatment* or refractory* or separation or social*) adj3 Anxi*).ti,ab,kf,ot. or GAD.ti,ab,kf,ot. 96563
3. Anxiety.ab. /freq=2 145610
4. *Panic Disorder/ or (Panic* adj4 (Disorder* or Attack*)).ti,ab,kf,ot. 13730
5. *Phobic Disorders/ or *Agoraphobia/ or *Kinesiophobia/ or *Phobia, Social/ or (Phobi* adj3 (Disorder* or Neuros* or Crowds or Open Spaces or Movement or Social)).ti,ab,kf,ot. 14293
6. phobi*.ti,kf. or phobi*.ab. /freq=2 or Scolionophobia*.ti,ab,kf,ot. or Claustrophobia*.ti,ab,kf,ot. or Agoraphobia*.ti,ab,kf,ot. or Kinesophobia*.ti,ab,kf,ot. or Sociophobia*.ti,ab,kf,ot. or Kinetophobia*.ti,ab,kf,ot. or ((Pain-Related Activit* or Pain Related Activit*) adj2 Avoid*).ti,ab,kf,ot. or Fear of Movement.ti,ab,kf,ot. or Movement Fear.ti,ab,kf,ot. or Fear of Social Evaluation.ti,ab,kf,ot. or Social Evaluation Fear.ti,ab,kf,ot. 12017
7. *Mutism/ or Kussmaul* Aphasia*.ti,ab,kf,ot. or ((Selective or Voluntary or Elective or Organic or Conversion) adj3 Mutism*).ti,ab,kf,ot. 1063
8. *"Bipolar and Related Disorders"/ or *Bipolar Disorder/ or (Bipolar* adj4 (disorder* or Psychos* or Depress*)).ti,ab,kf,ot. or (Manic* adj3 (Depress* or Psychos* or Disorder*)).ti,ab,kf,ot. or Manic-Depress*.ti,ab,kf,ot. 60384
9. *Cyclothymic Disorder/ or Cyclothymi*.ti,ab,kf,ot. 1261
10. *Depressive Disorder/ or Melancholia*.ti,ab,kf,ot. 57209
11. (depression or depressive or depressed).ab. /freq=2 291160
12. (depress* adj3 (syndrom* or patient* or individual* or adult* or child* or adolescen* or person* or men or women or male* or female* or seasonal or winter)).ti,ab,kf,ot. 120763
13. *Depressive Disorder, Major/ or (Involutional adj3 (Paraphrenia* or Psychos* or Depress* or Melancholia*)).ti,ab,kf,ot. or MDD.ti,ab,kf,ot. 45446
14. *Depressive Disorder, Treatment-Resistant/ or ((Treatment-resistant or resistant or Refractory* or Therapy-Resistant) adj4 Depress*).ti,ab,kf,ot. 8095
15. *Dysthymic Disorder/ or Dysthymia*.ti,ab,kf,ot. or ((Dysthymi* or Chronic or Neurotic or Persistent) adj4 (Depress* or Disorder*)).ti,ab,kf,ot. 61289
16. *Premenstrual Dysphoric Disorder/ or PMDD.ti,ab,kf,ot. or Premenstrual Dysphori*.ti,ab,kf,ot. 1439
17. ((menstru* or premenstru* or pms*) adj5 (depress* or dysphor*)).ti,ab,kf,ot. 1968
18. *Seasonal Affective Disorder/ 1070
19. *Vascular Depression/ or ((Subcortical or Ischemic or Vascular) adj3 Depress*).ti,ab,kf,ot. 1715
20. *Depression, Postpartum/ or ((Postnatal or Post-Partum or Post Partum or Postpartum or Post-Natal or Post Natal) adj4 (Depress* or Dysphori*)).ti,ab,kf,ot. 13572
21. or/1-20 582543
22. *Cannabidiol/ or *Cannabinoids/ or *Cannabinol/ or *Cannabis/ or *Dronabinol/ or *Endocannabinoids/ or *Medical Marijuana/ or *Marijuana Smoking/ 33844
23. (cannabi* or mari?uana or hashish or hash or ganja? or hemp or bhang or charas or endocannabinoid* or endo-cannabinoid* or phytocannabi* or phyto-cannabi*).ab. /freq=2 or (cannabi* or mari?uana or hashish or hash or ganja? or hemp or bhang or charas or endocannabinoid* or endo-cannabinoid* or phytocannabi* or phyto-cannabi*).ti,kf,nm. 62992
24. (CBD or CBDA or CBDV or GWP42006 or

GWP-42006).ab. /freq=2 or (CBD or CBDA or CBDV or GWP42006 or GWP-42006).ti,kf,nm. 10267

25. (THC* or tetrahydr?cannabi* or tetra-hydr?cannabi*).ab. /freq=2 or (THC* or tetrahydr?cannabi* or tetra-hydr?cannabi*).ti,kf,nm. 14492
26. (Cesamet* or Canemes* or Cesametic or Nabilone or “Lilly 109514” or Lilly109514 or “LY 109514” or LY109514 or cpd109514 or cpd-109514).af. 432
27. (Dexanabinol* or Hu-210 or hu210 or Hu-211 or hu211 or ETS2101).af. 542
28. (Dronabinol* or Marinol* or Syndros* or Reduvo* or Adversa or Ronabin or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924).af. 9402
29. (Epidiolex* or Epidyolex*).af. 225
30. Levonantradol.af. 72
31. (Nabiximols* or Nabidiolex* or Sativex* or NanaBis or Tetrabinex or “GW-1000” or gw1000 or SAB-378 or sab378).af. 484
32. (Bedica* or Bediol* or Bedrobinol* or Bedrocan* or Bedrolite*).af. 69
33. or/22-32 76520
34. 21 and 33 4261
35. (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti. 2184845
36. 34 not 35 3731
37. limit 36 to (english language and yr=”2024 -Current”) 491

Cochrane CENTRAL (via Ovid)

EBM Reviews - Cochrane Central Register of Controlled Trials <March 2025>

1. *Cannabidiol/ or *Cannabinoids/ or *Cannabinol/ or *Cannabis/ or *Dronabinol/ or *Endocannabinoids/ or *Medical Marijuana/ or *Marijuana Smoking/ 7
2. (cannabi* or mari?uana or hashish or hash or ganja? or hemp or bhang or charas or endocannabinoid* or endo-cannabinoid* or phytocannabi* or phyto-cannabi*).ab. /freq=2 or (cannabi* or mari?uana or hashish or hash or ganja? or hemp or bhang or charas or endocannabinoid* or endo-cannabinoid* or phytocannabi* or phyto-cannabi*).ti,kf. 4663
3. (CBD or CBDA or CBDV or GWP42006 or GWP-42006).ab. /freq=2 or (CBD or CBDA or CBDV or GWP42006 or GWP-42006).ti,kf. 1422
4. (THC* or tetrahydr?cannabi* or tetra-hydr?cannabi*).ab. /freq=2 or (THC* or tetrahydr?cannabi* or tetra-hydr?cannabi*).ti,kf. 1875
5. (Cesamet* or Canemes* or Cesametic or Nabilone or “Lilly 109514” or Lilly109514 or “LY 109514” or LY109514 or cpd109514 or cpd-109514).af. 164
6. (Dexanabinol* or Hu-210 or hu210 or Hu-211 or hu211 or ETS2101).af. 8
7. (Dronabinol* or Marinol* or Syndros* or Reduvo* or Adversa or Ronabin or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924).af. 1184
8. (Epidiolex* or Epidyolex*).af. 95
9. Levonantradol.af. 12
10. (Nabiximols* or Nabidiolex* or Sativex* or NanaBis or Tetrabinex or “GW-1000” or gw1000 or SAB-378 or sab378).af. 227
11. (Bedica* or Bediol* or Bedrobinol* or Bedrocan* or Bedrolite*).af. 23
12. or/1-11 6083
13. *Mood Disorders/ or ((Mood or Affective) adj2 Disorder*).af. 6701
14. *Anxiety Disorders/ or *Anxiety, Separation/ or ((Persistent or Disabling or disorder* or neuros* or neurotic or treatment* or refractory* or separation or social*) adj3 Anxi*).af. or GAD.af. 29607
15. Anxiety.ab. /freq=2 38604
16. *Panic Disorder/ or (Panic* adj4 (Disorder* or Attack*)).af. 2826
17. *Phobic Disorders/ or *Agoraphobia/ or *Kinesiophobia/ or *Phobia, Social/ or (Phobi* adj3 (Disorder* or Neuros* or Crowds or Open Spaces or Movement or Social)).af. 3276
18. phobi*.ti,kf. or phobi*.ab. /freq=2 or Scolionophobia*.af. or Claustrophobia*. af. or Agoraphobia*.af. or Kinesophobia*. af. or Sociophobia*.af. or Kinetophobia*. af. or ((Pain-Related Activit* or Pain Related Activit*) adj2 Avoid*).af. or Fear of Movement. af. or Movement Fear.af. or Fear of Social Evaluation.af. or Social Evaluation Fear.af. 3420
19. *Mutism/ or Kussmaul* Aphasia*.af. or

((Selective or Voluntary or Elective or Organic or Conversion) adj3 Mutism*).af. 44

20. *"Bipolar and Related Disorders"/ or *Bipolar Disorder/ or (Bipolar* adj4 (disorder* or Psychos* or Depress*)).af. or (Manic* adj3 (Depress* or Psychos* or Disorder*)).af. or Manic-Depress*.af. 8410
21. *Cyclothymic Disorder/ or Cyclothymi*.af. 70
22. *Depressive Disorder/ or Melancholia*.af. 234
23. (depression or depressive or depressed).ab. / freq=2 56042
24. (depress* adj3 (syndrom* or patient* or individual* or adult* or child* or adolescen* or person* or men or women or male* or female* or seasonal or winter)).af. 47790
25. *Depressive Disorder, Major/ or (Involutional adj3 (Paraphrenia* or Psychos* or Depress* or Melancholia*)).af. or MDD.af. 5386
26. *Depressive Disorder, Treatment-Resistant/ or ((Treatment-resistant or resistant or Refractory* or Therapy-Resistant) adj4 Depress*).af. 2644
27. *Dysthymic Disorder/ or Dysthymia*.af. or ((Dysthymi* or Chronic or Neurotic or Persistent) adj4 (Depress* or Disorder*)).af. 8346
28. *Premenstrual Dysphoric Disorder/ or PMDD.af. or Premenstrual Dysphori*.af. 369
29. ((menstru* or premenstru* or pms*) adj5 (depress* or dysphor*)).af. 528
30. *Seasonal Affective Disorder/ 34
31. *Vascular Depression/ or ((Subcortical or Ischemic or Vascular) adj3 Depress*).af. 274
32. *Depression, Postpartum/ or ((Postnatal or Post-Partum or Post Partum or Postpartum or Post-Natal or Post Natal) adj4 (Depress* or Dysphori*)).af. 3112
33. or/13-32 117194
34. 12 and 33 704
35. (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti. 5403
36. 34 not 35 704
37. limit 36 to (conference proceeding or dissertation thesis or preprint or trial registry record) 349
38. 36 not 37 355
39. limit 38 to (yr="2024 -Current" and english language) 50

PsycInfo (via Ovid)

APA PsycInfo <1806 to April 2025 Week 4>

1. *Cannabidiol/ or *Cannabinoids/ or *Cannabinol/ or *Cannabis/ or *Dronabinol/ or *Endocannabinoids/ or *Medical Marijuana/ or *Marijuana Smoking/ 12712
2. (cannabi* or mari?uana or hashish or hash or ganja? or hemp or bhang or charas or endocannabinoid* or endo-cannabinoid* or phytocannabi* or phyto-cannabi*).ab. / freq=2 or (cannabi* or mari?uana or hashish or hash or ganja? or hemp or bhang or charas or endocannabinoid* or endo-cannabinoid* or phytocannabi* or phyto-cannabi*).ti. 23285
3. (CBD or CBDA or CBDV or GWP42006 or GWP-42006).ab. /freq=2 or (CBD or CBDA or CBDV or GWP42006 or GWP-42006).ti. 1279
4. (THC* or tetrahydr?cannabi* or tetra-hydr?cannabi*).ab. /freq=2 or (THC* or tetrahydr?cannabi* or tetra-hydr?cannabi*).ti. 2951
5. (Cesamet* or Canemes* or Cesametic or Nabilone or "Lilly 109514" or Lilly109514 or "LY 109514" or LY109514 or cpd109514 or cpd-109514).af. 779
6. (Dexanabinol* or Hu-210 or hu210 or Hu-211 or hu211 or ETS2101).af. 747
7. (Dronabinol* or Marinol* or Syndros* or Reduvo* or Adversa or Ronabin or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924).af. 2731
8. (Epidiolex* or Epidyolex*).af. 105
9. Levonantradol.af. 78
10. (Nabiximols* or Nabidiolex* or Sativex* or NanaBis or Tetrabinex or "GW-1000" or gw1000 or SAB-378 or sab378).af. 696
11. (Bedica* or Bediol* or Bedrobinol* or Bedrocan* or Bedrolite*).af. 21
12. or/1-11 25964
13. *Mood Disorders/ or *"Mental Disorders due to General Medical Conditions"/ or ((Mood or Affective) adj2 Disorder*).id,jx,ti,tc. 39032
14. *Generalized Anxiety Disorder/ or *Separation Anxiety Disorder/ or ((Persistent or Disabling or disorder* or neuros* or neurotic or

treatment* or refractory* or separation or social*) adj3 Anxi*).id,jx,ti,tc. or GAD.id,jx,ti,tc. 36162

15. Anxiety.ab. /freq=2 121200
16. *Panic Attack/ or *Panic Disorder/ or (Panic* adj4 (Disorder* or Attack*)).id,jx,ti,tc. 9492
17. *Phobias/ or *Acrophobia/ or *Agoraphobia/ or *Claustrophobia/ or *Ophidiophobia/ or *School Phobia/ or *Social Phobia/ or (Phobi* adj3 (Disorder* or Neuros* or Crowds or Open Spaces or Movement or Social)).id,jx,ti,tc. 13535
18. phobi*.ti. or phobi*.ab. /freq=2 or Scolionophobia*.id,jx,ti,tc. or Claustrophobia*. id,jx,ti,tc. or Agoraphobia*.id,jx,ti,tc. or Kinesophobia*.id,jx,ti,tc. or Sociophobia*. id,jx,ti,tc. or Kinetophobia*.id,jx,ti,tc. or ((Pain-Related Activit* or Pain Related Activit*) adj2 Avoid*).id,jx,ti,tc. or Fear of Movement. id,jx,ti,tc. or Movement Fear.id,jx,ti,tc. or Fear of Social Evaluation.id,jx,ti,tc. or Social Evaluation Fear.id,jx,ti,tc. 11044
19. *Selective Mutism/ or *Elective Mutism/ or Kussmaul* Aphasia*.id,jx,ti,tc. or ((Selective or Voluntary or Elective or Organic or Conversion) adj3 Mutism*).id,jx,ti,tc. 700
20. *Bipolar Disorder/ or *Mania/ or *Hypomania/ or *Bipolar I Disorder/ or *Bipolar II Disorder/ or *Manic Depression/ or (Bipolar* adj4 (disorder* or Psychos* or Depress*)).id,jx,ti,tc. or (Manic* adj3 (Depress* or Psychos* or Disorder*)).id,jx,ti,tc. or Manic-Depress*. id,jx,ti,tc. 38254
21. *Cyclothymic Disorder/ or Cyclothymi*. id,jx,ti,tc. 636
22. Melancholia*.id,jx,ti,tc. 1421
23. (depression or depressive or depressed).ab. / freq=2 214076
24. (depress* adj3 (syndrom* or patient* or individual* or adult* or child* or adolescen* or person* or men or women or male* or female* or seasonal or winter)).id,jx,ti,tc. 41658
25. *Major Depression/ or (Involutional adj3 (Paraphrenia* or Psychos* or Depress* or Melancholia*)).id,jx,ti,tc. or MDD.id,jx,ti,tc. 140140
26. *Treatment Resistant Depression/ or *Tricyclic Resistant Depression/ or ((Treatment-resistant or resistant or Refractory* or Therapy-Resistant) adj4 Depress*).id,jx,ti,tc. 4181
27. *Dysthymic Disorder/ or Dysthymia*.id,jx,ti,tc. or ((Dysthymi* or Chronic or Neurotic or Persistent) adj4 (Depress* or Disorder*)). id,jx,ti,tc. 8040
28. *Premenstrual Dysphoric Disorder/ or PMDD. id,jx,ti,tc. or Premenstrual Dysphori*.id,jx,ti,tc. 757
29. ((menstru* or premenstru* or pms*) adj5 (depress* or dysphor*)).id,jx,ti,tc. 903
30. *Anaclitic Depression/ or *Endogenous Depression/ or *Reactive Depression/ or *Recurrent Depression/ or *Late Life Depression/ or *Seasonal Affective Disorder/ or *Winter Depression/ or *Disruptive Mood Dysregulation Disorder/ or *Agitated Depression/ or *Unipolar Depression/ or *Atypical Depression/ 143036
31. ((Subcortical or Ischemic or Vascular) adj3 Depress*).id,jx,ti,tc. 295
32. *Postpartum Depression/ or *Postnatal Depression/ or *Puerperal Depression/ or ((Postnatal or Post-Partum or Post Partum or Postpartum or Post-Natal or Post Natal) adj4 (Depress* or Dysphori*)).id,jx,ti,tc. 6910
33. or/13-32 385610
34. 12 and 33 2322
35. (animal or animals or bovine or canine or dog or dogs or hens or mice or mouse or pig or pigs or rabbit or rabbits or rat or rats or rattus or veterinary or zebrafish).ti. 161598
36. 34 not 35 2081
37. limit 36 to (english language and yr="2024 -Current") 141

ClinicalTrials.gov Search Strategy

We searched ClinicalTrials.gov for ongoing studies using the search: (marijuana OR cannabi* OR epidiolex OR endocannabi* OR THC OR tetrahydrocannabi* OR cesamet OR dexanabinol OR phytocannab* OR CBD OR Dronabinol OR Marinol OR Syndros OR Nabiximols OR Nabidiolex OR Sativex OR Bedica OR Bediol OR Bedrobinol) AND AREA[ConditionSearch] (depression OR bipolar OR anxiety OR phobia OR panic OR mood disorder* OR seasonal affective disorder OR winter depression OR premenstrual dysmorphi* OR PMDD OR mutism OR mania OR manic-depess*)

Detailed Inclusion and Exclusion Criteria

Table A1. Detailed Inclusion and Exclusion Criteria

Key Question	What are the effects of cannabis on health outcomes and healthcare utilization for adults with anxiety or mood disorder? *Do the effects differ by patient characteristics, such as age or presence of comorbidities?*	
	INCLUDE	EXCLUDE
Population	Adults with a diagnosis of anxiety or mood disorder, as defined in the DSM-5: • Anxiety disorders ◦ Generalized anxiety disorder (GAD) ◦ Social anxiety disorder ◦ Panic disorder ◦ Agoraphobia ◦ Substance/medication-induced anxiety disorder ◦ Specific phobia ◦ Separation anxiety disorder ◦ Selective mutism ◦ Anxiety disorder due to another medical condition ◦ Other specified anxiety disorder ◦ Unspecified anxiety disorder • Mood disorders • Bipolar and related disorders ◦ Bipolar I disorder ◦ Bipolar II disorder ◦ Cyclothymic disorder ◦ Substance/medication-induced bipolar and related disorder ◦ Bipolar and related disorder due to another medical condition ◦ Other specified bipolar and related disorder ◦ Unspecified bipolar and related disorder • Depressive disorders ◦ Disruptive mood dysregulation disorder ◦ Major depressive disorder, single and recurrent episodes ◦ Persistent depressive disorder (dysthymia) ◦ Premenstrual dysphoric disorder ◦ Substance/medication-induced depressive disorder ◦ Depressive disorder due to another medical condition ◦ Other specified depressive disorder ◦ Unspecified depressive disorder Studies with mixed age (adult and aged under 18 years) population may be included, if results are reported by age group	• People aged < 18 • Adults who are pregnant • Adults with a primary diagnosis other than those listed

Key Question	What are the effects of cannabis on health outcomes and healthcare utilization for adults with anxiety or mood disorder? *Do the effects differ by patient characteristics, such as age or presence of comorbidities?*	
Intervention	Cannabis preparations, including marijuana, hashish, tincture, hashish oil, infusion, and plant extract (including Epidiolex – an FDA-approved medication containing cannabidiol, and nabiximols [brand-name: Sativex] – a nonsynthetic pharmaceutical product with a standard composition and dosage) or FDA-approved synthesized, pharmaceutically prepared cannabinoids (Dronabinol) [brand-names: Marinol and Syndros], Nabilone [brand-name: Cesamet]), alone or in combination with other intervention(s). All methods of administration (e.g., smoking, vaping, edibles). The use of cannabis in combination with other interventions (e.g., psychosocial, medication) will be included if the effect of cannabis can be isolated (i.e., all participants receive the additional interventions).	Other synthesized cannabinoids (e.g., synthetic marijuana, spice, K2)
Comparator	Any other intervention or a non-exposed control group	• Studies with no comparison group
Outcomes	Anxiety or mood disorder symptoms using validated tools such as: • Beck Anxiety Inventory • Young Mania Rating Scale • Hamilton Depression Rating Scale (HAM-D) Relapse and remission of anxiety or mood disorders Global improvement, using validated tools such as: • Clinical Global Impression of Change Use of other medications for anxiety or mood disorders Quality of life, using validated tools such as: • EQ-5D Social functioning (e.g., ability to work) Sleep quality, using validated tools such as: • Pittsburgh Sleep Quality Index Utilization of health services AEs and SAEs Study dropout due to AEs	• Laboratory, blood, or imaging findings • Outcomes other than those listed
Timing	Short- and long-term outcomes Only including efficacy outcomes reported at 4 weeks and longer	• Outcomes of interest reported for a duration of shorter than 4 weeks
Setting	Any setting, except laboratory conditions	• Laboratory-based studies
Study design	Controlled clinical trials (randomized or non-randomized), and methodologically rigorous observational studies with a comparison group (case control/cohort studies) that adjust for important confounders	• Any other study design

Abbreviations. AEs: adverse events; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EQ-5D: EuroQol-5D; FDA: US Food and Drug Administration; SAE: serious adverse event.

Participant Characteristics and Association with Outcomes

When discussing risk and protective factors or variables in statistical models, in almost all cases, we are referring to associations of participant characteristics with outcomes and not causation of outcomes. This is important because participant characteristics, such as race and ethnicity, serve as proxy or surrogate measures for underlying etiological factors not measured or evaluated in analyses. Etiological factors that might cause differences in outcomes for subgroups of participants could include systemic racism or other forms of systemic discrimination, stress, poverty, housing instability, or epigenetics. For example, by describing any differences in outcomes by race and ethnic groups, we are noting observed associations; these associations are not caused by biological determinants of being Black, White, or Hispanic.

Risk of Bias Assessment

Two independent researchers conducted risk-of-bias (RoB) assessments using standard instruments adapted from those used by national and international organizations;[29-32] conflicts were handled through discussion. [33,34]

Randomized Controlled Trials

Low-risk-of-bias randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Low-risk-of-bias randomized controlled trials also have low potential for bias from conflicts of interest and funding source(s). Moderate-risk-of-bias randomized controlled trials have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. High-risk-of-bias randomized controlled trials have clear flaws that could introduce significant bias.

Quasi-experimental Studies

Low-risk-of-bias quasi-experimental studies have a control group that is unexposed to the intervention being studied; methods are in place to prevent contamination bias; pre- and post-measures are done concurrently; and participant characteristics are balanced between groups or controlled for by propensity scores, by statistical adjustment, or both. Moderate-risk-of-bias quasi-experimental studies have incomplete information about methods that might mask important limitations, a meaningful conflict of interest, or are at risk for contamination bias. High-risk-of-bias quasi-experimental studies do not have a control group (i.e., before and after studies or interrupted time series) or have other clear flaws that could introduce significant bias.

Cohort Studies

Low-risk-of-bias cohort studies include a sample that is representative of the source population, have low loss to follow-up, and measure and consider relevant confounding factors. Low-risk-of-bias cohort studies also list their funding source(s) and have a low potential of bias from conflicts of interest. Moderate-risk-of-bias cohort studies might not have measured all relevant confounding factors or adjusted for them in statistical analyses, have loss to follow-up that could bias findings, consist of a sample that is not representative of the source population, or have potential conflicts of interest that are not addressed. High-risk-of-bias cohort studies have a clear, high RoB that would affect findings.

Cross-sectional Studies

Cross-sectional studies are hypothesis-generating studies and lack the temporal nature of a design to assess causal relationships. This study design is vulnerable to a high RoB. As a result, all cross-sectional studies are rated as having high RoB.

Certainty of Evidence Assessment

We assigned each outcome a summary judgment for the overall certainty of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[33,34] Two experienced independent researchers assigned ratings, with disagreements resolved by discussion. The GRADE system defines the overall certainty of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed NRSs with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially

different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or NRSs without special strengths.

- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are NRSs with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables and Risk of Bias Tables

Table B1. Study Characteristics

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Anxiety disorders								
Gundugurti et al., 2025[35] Outpatient India Multi-site Moderate RoB	CBD (150-300mg/mL bid) nanodispersible oral solution	Matched placebo	RCT	Adults with mild to moderate ICD-11 GAD	Included if: • Age 18-65 • ICD-11 GAD • Mild to moderate anxiety scores • Female patients non-pregnant and non-lactating with adequate protection from conception • Biochemistry and medical tests within normal ranges. Excluded if: • Hepatic, hematological, renal, cardiovascular, gastrointestinal, immunological, or pulmonary diseases or ongoing malignancies, epilepsy. • Alcohol and/or drug dependence, substance abuse, suicidal ideation, manic/bipolar disorders, OCD, PTSD, psychosis, factitious disorder or somatoform disorder, schizophrenia, depression • Concomitant medications known to have interactions with CBD • After placebo run-in period, if there was any change from the screening score (GAD-7, HAM-A, CGI-I, CGI-S, PHQ-9, and PSQI) >= 25% from baseline	89	89	Age: 37 years (10) CBD; 37 years (11) placebo Female: 33/89 (37%) CBD; 32/89 (36%) placebo Race/ethnicity, insurance status, comorbidities, Veteran status not reported No other substance use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Bidwell et al., 2024[37] Participants recruited from the community US Single-site High RoB	cannabis flower product groups: THC-dominant, 1:1 THC:CBD, or CBD-dominant ad libitum for 4 weeks	Non cannabis users	Quasi-experimental study, with an observational substudy	Adults with mild anxiety (≥ 5 on GAD-7 scale)	Included if: • Between 21 and 70 years of age • Report at least mild anxiety symptoms (~5 on GAD-7) • Have used marijuana at least once and desire to use marijuana to cope with anxiety (cannabis groups) • Not used marijuana for past six months and not have a desire to use marijuana to cope with anxiety (non-use group) • Report not using drugs of abuse (e.g., cocaine, methamphetamine) in past 72 hours and test negative for drugs of abuse on a urine toxicology test at the Baseline visit • Not be using psychotropic, steroid-based medications, or maximal doses of non-steroidal anti-inflammatories (NSAIDs), however, anti-depressants and ADHD medications are allowed • Not have immune-relevant disease (e.g., HIV) or be using anti-viral medications • Not be a regular tobacco user (<=4 days per week) • Have a breath alcohol level of 0.00 at the Baseline visit • Not be actively seeking or in treatment for any substance use disorder • Female subjects must not be or trying to become pregnant (as indicated by a Pregnancy test administered at Baseline) • Not in treatment for or have a history of psychotic disorder, bipolar disorder, or major depression disorder with suicidal ideation	THC-dominant: 105 1:1 THC:CBD: 95 CBD-dominant: 117	44	Note. characteristics only provided for those who completed. Age: non-use: 35.29 (14.35) THC + CBD: 32.28 (12.51) CBD: 29.53 (10.86) THC: 31.27 (11.69) p = .08 Female, n (%): non-use: 27 (64.3%) THC + CBD: 45 (56.2%) CBD: 47 (51.1%) THC: 50 (58.1%) p = 0.64 Race/ethnicity, n (%): non-use: American Indian or Alaska Native: 2 (4.8%) Asian: 5 (11.9%) African American or Black: 1 (2.4%) Hispanic or Latino: 4 (9.5%) More than one race/ethnicity: 0 (0.0%) White: 29 (69.0%) Prefer not to answer: 1 (2.4%) THC + CBD: American Indian or Alaska Native: 3 (3.8%) Asian: 3 (3.8%) African American or Black: 4 (5.0%) Hispanic or Latino: 4 (5.0%) More than one race/ethnicity: 2 (2.5%) White: 62 (77.5%) Prefer not to answer: 2 (2.5%)

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
					Excluded if: • Tobacco use • Low generalized anxiety disorder score • Psychiatric diagnosis • Substance use disorder • Psychotropic medication use • No desire to use cannabis • Steroid-based medication • No lifetime cannabis use • Anti-viral medication use • Other non-medical drug use • Pregnant or trying to become pregnant • Lives too far away or other logistical issue • Serious medical illness or other safety concern			CBD: American Indian or Alaska Native: 1 (1.1%) Asian: 6 (6.5%) African American or Black: 3 (3.3%) Hispanic or Latino: 5 (5.4%) More than one race/ethnicity: 0 (0.0%) White: 72 (78.3%) Prefer not to answer: 5 (5.4%) THC: American Indian or Alaska Native: 2 (2.3%) Asian: 7 (8.1%) African American or Black: 4 (4.7%) Hispanic or Latino: 7 (8.1%) More than one race/ethnicity: 3 (3.5%) White: 60 (69.8%) Prefer not to answer: 3 (3.5%) $p < .001$ Insurance status, Veteran status, other comorbidities NR
Fabre et al., 1978[6] Psychiatric clinic US Single site High risk of bias	Nabilone (1 mg 3 times a day; capsule) for 4 weeks	Placebo	To assess the effectiveness of nabilone in the treatment of anxiety CCT	Adults with anxiety	Included if: • Aged 18 to 60 • No risk of pregnancy • Duration of anxiety such that spontaneous remission would not occur Excluded if: • Psychosis • Organic CNS disease • Alcohol or drug addiction • Other significant disease • History of adverse drug reactions or severe plant allergies	10	10	Note. Patient characteristics not reported by group Mean age (range): 29.0 years (19 to 41) Female: 5 of 20 (25%) Race/ethnicity: 19 of 20 (95.5%) White; 1 of 10 (5.0%) Black

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Kwee et al., 2022[7,9] Mental health care centers The Netherlands Multi-site Moderate risk of bias	300 mg CBD (powder, purity of greater than 99.9%) per dose in 8 treatment sessions Administered approximately 2 hours before exposure therapy Delivered in 8 90-min therapist-assisted augmented exposure sessions Delivered by psychologists trained in CBT and in the standardized protocols for exposure therapy used in the study	Placebo (lactose)	To determine whether augmentation of exposure therapy with 300 mg oral CBD would lead to stronger or faster improvement of anxiety symptoms RCT	Adults with social anxiety disorder or panic disorder with agoraphobia	Included if: • Aged between 18 and 65 years • Primary diagnosis of social anxiety disorder or panic disorder with agoraphobia according to DSM-IV criteria Excluded if: • Co-morbid psychiatric disorders, i.e., current severe major de- pressive (BDI > 40) or bipolar disorder, psychosis, dependence of alcohol and drugs • Use of antipsychotic medication • Regular daytime use of benzodiazepines • Changes in dosing regimen of serotonergic antidepressants < 4 weeks prior to study entry • Use of recreational drugs < 2 months preceding study entry (alcohol and tobacco permitted) • Pregnant or breastfeeding	39	41	Mean age (SD): 34.9 years (9.3) CBD; 38.3 years (11.3) placebo Female: 17 of 39 (43.6%) CBD; 15 of 41 (36.6%) placebo Race/ethnicity not reported Received previous treatment: 23 of 39 (63.9%) CBD; 26 of 41 (66.7%) placebo Use of antidepressant medication: 18 of 39 (46.2%) CBD; 16 of 41 (39.0%) placebo Primary diagnosis of social anxiety disorder: 18 of 39 (46.2%) CBD; 19 of 41 (46.3%) placebo Primary diagnosis of panic disorder with agoraphobia: 21 of 39 (53.8%) CBD; 22 of 41 (53.7%) placebo

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Masataka, 2019[8] Hospitals in the Osaka prefecture Japan Multi-site High risk of bias	300 mg CBD (RSHO-X hemp oil, HempMeds USA) Oil did not contain any THC, terpenes, or other cannabinoids Administered 300 mg daily for 4 weeks Delivered via oral syringe by a clinical psychologist who visited the participants in their home	Olive oil	To assess the efficacy of CBD treatment for young adults with social anxiety disorder RCT	Young adults with social anxiety disorder	Included if: • Diagnosis of social anxiety disorder • Naive to cannabis Excluded if: • Experience of receiving previous or concurrent psychological or drug treatment • Any form of psychotic or organic illness • Diagnosis of cluster A or B personality disorder • Acute suicidality • Drug and alcohol dependence • Comorbid diagnosis of other anxiety or mood disorders	20	20	Age not reported; all aged 18 or 19 Female: 5 of 20 (25.0%) CBD; 6 of 20 (30.0%) placebo Race/ethnicity not reported Receiving CBT: 0

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Depressive disorders								
Feingold et al., 2017[10] Population US Multi-site Moderate risk of bias	Cannabis use (any use between Wave 1 and 2 of NESARC) without a diagnosis of CUD Cannabis use (any use between Wave 1 and 2 of NESARC) with a diagnosis of CUD	No cannabis use (between Wave 1 and 2 of NESARC)	To explore the effect of cannabis use and CUD on the course and outcome of MDD over a 3-year period Prospective, national population survey	Adults with a past-year diagnosis of MDD in Wave 1 who also participated in Wave 2	Included if: • Past-year diagnosis of MDD at Wave 1 (defined as presence of at least 5 out of 9 symptoms during the same 2-week period in the last 12 months) Excluded if: • Substance-induced mental disorders	173 who used cannabis without CUD 121 who used cannabis who also had CUD	2,283 who did not use cannabis	Age: 77 of 173 (46.8%) aged 18 to 29, 62 of 173 (31.0%) aged 30 to 44, 34 of 173 (22.3%) aged 45 to 64, 0 aged 65 and older, cannabis use without CUD; 76 of 121 (65.9%) aged 18 to 29, 32 of 121 (25.6%) aged 30 to 44, 13 of 121 (8.5%) aged 45 to 64, 0 aged 65 and older, cannabis use with CUD; 586 of 2,283 (27.0%) aged 18 to 29, 783 of 2,283 (33.7%) aged 30 to 44, 736 of 2,283 (33.0%) aged 45 to 64, 178 of 2,283 (6.2%) aged 65 and older, cannabis use without CUD Female: 95 of 173 (49.2%) cannabis use without CUD; 65 of 121 (57.4%) cannabis use with CUD; 1,679 of 2,283 (69.6%) no cannabis use Race/ethnicity: 123 of 173 (77.3%) White, 21 of 173 (8.8%) Black, 8 of 173 (7.2%) American Indian or Alaska Native, 1 of 173 (0.3%) Asian, Native Hawaiian or Pacific Islander, 20 of 173 (6.4%) Hispanic or Latino, cannabis use without CUD; 69 of 121 (72.2%) White, 22 of 121 (13.0%) Black, 3 of 121 (2.9%) American Indian or Alaska Native, 3 of 121 (2.8%) Asian, Native Hawaiian or Pacific Islander, 24 of 121 (9.1%)

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Hispanic or Latino, cannabis use with CUD; 1,419 of 2,283 (75.9%) White, 356 of 2,283 (9.0%) Black, 63 of 2,283 (3.5%) American Indian or Alaska Native, 41 of 2,283 (2.8%) Asian, Native Hawaiian or Pacific Islander, 404 of 2,283 (8.8%) Hispanic or Latino, no cannabis use Any SUD: 72 of 173 (43.1%) cannabis use without CUD; 74 of 121 (59.5%) cannabis use with CUD; 324 of 2,283 (14.3%) no cannabis use Any psychiatric disorder explored: 143 of 173 (81.3%) cannabis use without CUD; 104 of 121 (83.3%) cannabis use with CUD; 1,517 of 2,283 (67.7%) no cannabis use Any mood disorder: 66 of 173 (38.7%) cannabis use without CUD; 48 of 121 (41.5%) cannabis use with CUD; 669 of 2,283 (29.0%) no cannabis use Dysthymia: 34 of 173 (19.9%) cannabis use without CUD; 24 of 121 (19.0%) cannabis use with CUD; 362 of 2,283 (15.3%) no cannabis use Manic episode: 26 of 173 (13.8%) cannabis use without CUD; 23 of 121 (19.5%) cannabis use with CUD; 271 of 2,283 (11.9%) no cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Hypomanic episode: 18 of 173 (11.0%) cannabis use without CUD; 10 of 121 (9.1%) cannabis use with CUD; 94 of 2,283 (4.1%) no cannabis use Any anxiety disorder: 61 of 173 (34.1%) cannabis use without CUD; 46 of 121 (43.0%) cannabis use with CUD; 875 of 2,283 (40.9%) no cannabis use Panic disorder: 25 of 173 (11.6%) cannabis use without CUD; 21 of 121 (18.4%) cannabis use with CUD; 282 of 2,283 (12.7%) no cannabis use Specific phobia: 31 of 173 (19.9%) cannabis use without CUD; 30 of 121 (28.1%) cannabis use with CUD; 419 of 2,283 (19.1%) no cannabis use Social phobia: 31 of 173 (19.9%) cannabis use without CUD; 30 of 121 (28.1%) cannabis use with CUD; 282 of 2,283 (13.5%) no cannabis use GAD: 31 of 173 (14.4%) cannabis use without CUD; 18 of 121 (18.8%) cannabis use with CUD; 351 of 2,283 (16.6%) no cannabis use Any personality disorder: 83 of 173 (47.1%) cannabis use without CUD; 69 of 121 (55.5%) cannabis use with CUD; 803 of 2,283 (36.3%) no cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Avoidant personality disorder: 31 of 173 (17.7%) cannabis use without CUD; 22 of 121 (17.6%) cannabis use with CUD; 293 of 2,283 (13.2%) no cannabis use Dependent personality disorder: 5 of 173 (4.9%) cannabis use without CUD; 7 of 121 (5.5%) cannabis use with CUD; 58 of 2,283 (2.6%) no cannabis use Paranoid personality disorder: 44 of 173 (24.0%) cannabis use without CUD; 39 of 121 (26.3%) cannabis use with CUD; 470 of 2,283 (20.1%) no cannabis use Schizoid personality disorder: 19 of 173 (10.9%) cannabis use without CUD; 25 of 121 (20.4%) cannabis use with CUD; 293 of 2,283 (12.3%) no cannabis use Histrionic personality disorder: 26 of 173 (16.1%) cannabis use without CUD; 17 of 121 (12.8%) cannabis use with CUD; 153 of 2,283 (6.9%) no cannabis use Antisocial personality disorder: 46 of 173 (28.9%) cannabis use without CUD; 32 of 121 (26.6%) cannabis use with CUD; 180 of 2,283 (9.1%) no cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Bipolar disorders								
Pinto et al., 2024[36] NCT03310593 Teaching hospital Single site Brazil Moderate RoB	Cannabidiol (150 to 300 mg/day) for 8 weeks	Matched placebo	A randomized, double-blind, placebo-controlled pilot study to assess the efficacy of adjunctive cannabidiol in bipolar depression	Participants with bipolar I or II disorder with a current major depressive episode	Included if: • 18 years or older • MADRS total score >=12, with scores on MADRS items 1 (apparent sadness) and 2 (reported sadness) >=2 at baseline • YMRS total score =<11 at baseline; (d) regular use of either lithium, valproate, or atypical antipsychotics at therapeutic levels for at least 4 weeks before baseline assessment • Able to provide informed consent and to comply with the study procedures • On an effective contraceptive method in the case of heterosexual women of childbearing age Excluded if: • Presence of another active major psychiatric disorder within 6 months before study entry that was requiring acute treatment at the screening or baseline assessment (currently causing more impairment than the depressive symptoms) assessed with MINI and according to DMS-5 criteria • Current or past drug sensitivity or intolerance to cannabidiol, assessed through clinical interview • Diagnosis of any substance use disorder according to DSM-5 criteria within past 6 months, except for nicotine, assessed with MINI	19	16	Age, mean (SD) CBD: 42.2 (13.8) Placebo: 45.9 (13.0) Gender, female (%) CBD: 13 (68.4) Placebo: 11 (68.8) Ethnicity, white (%) CBD: 15 (78.9) Placebo: 9 (56.3) Years of education, mean (SD) CBD: 11.6 (4.2) Placebo: 13.5 (3.7) Working or studying, yes (%) CBD: 9 (47.4) Placebo: 7 (43.8) Bipolar disorder type I, yes (%) CBD: 13 (68.4) Placebo: 11 (68.8) Past cannabis use, yes (%) CBD: 02 (10.5) Placebo: 04 (25.0) Current medication Lithium, yes (%) CBD: 10 (52.6) Placebo: 10 (62.5) Anticonvulsants, yes (%) CBD: 13 (68.4) Placebo: 8 (50.0) Antipsychotics, yes (%) CBD: 14 (73.7) Placebo: 11 (68.8) Antidepressants, yes (%) CBD: 13 (68.4) Placebo: 8 (50.0)

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
					• Clinically significant unstable medical illness, neurological disorders or inflammatory/ autoimmune diseases, or any autoimmune, inflammatory, or neurologic disorders that required treatment with steroidal anti-inflammatory medications or immunotherapy with biologic drugs at baseline • Current serious suicide risk or risk of injury to self or others as clinically judged by the psychiatrists as well as using the MINI • Being pregnant or breastfeeding, assessed through clinical interview and laboratory exams. Also, participants were not allowed to use cannabis during the clinical trial			
Baethge et al., 2008[11] Single hospital (international research center) US Single site Moderate risk of bias	Cannabis use	No cannabis use	To evaluate the sequencing of specific substance use and affective morbidity in people with bipolar disorder Nonrandomized, prospective, longitudinal study	Adults with bipolar disorder	Included if: • Aged 18 years and older • First-lifetime, DSM-IV diagnosis of manic or mixed episode of type I bipolar disorder • Consecutively admitted to a single hospital between 1989 and 1996 Excluded if: • Acute intoxication, withdrawal, or delirium • Previous hospitalization • Intellectual disability (IQ < 70) or organic mental disorder • Ill more than 1 year before intake • More than 3 months of prior antipsychotic or mood stabilizer treatment	30	136	Median age (range): 28 years (18 to 72) Female: 76 of 166 (45.8%) Race/ethnicity not reported Substance use disorder: 75 of 166 (45.2%) Alcohol use (beyond social drinking): 103 of 166 (62.0%) Mean number of major affective episodes per person per year (SD): 1.6 (1.1)

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
EMBLEM[17,19-21] Community (inpatient and outpatient units) Europe (14 countries) Multi-site Moderate risk of bias	Current cannabis use (defined as any use)	No cannabis use	To evaluate the outcome of pharmacological treatment in people with bipolar disorder Nonrandomized, prospective, comparative study	Adults with bipolar disorder	Included if: • Aged at least 18-years old • Acute manic or mixed episode within standard care • Initiated or changed oral medication for treatment of acute mania in bipolar disorder (antipsychotics, anticonvulsants and/or lithium; not antidepressants or benzodiazepines) Excluded if: • Enrolled in another interventional study	Data extracted from van Rossum et al.[17] 436	Data extracted from van Rossum et al.[17] 2,990	Data extracted from van Rossum et al.[17] Mean age (SD): 33.8 years (9.7) cannabis use; 46.2 years (13.1) no cannabis use Female: 140 of 436 (32.1%) cannabis use; 1,758 of 2,990 (58.8%) no cannabis use Race/ethnicity not reported Alcohol use: 80.3% cannabis use; 37.2% no cannabis use Other substance use: 34.3% cannabis use; 2.6% no cannabis use Inpatient: 56.1% cannabis use; 36.8% no cannabis use
Gruber et al., 2012[12] Community US Multi-site High risk of bias	Cannabis - smoking only	No cannabis use	To determine if marijuana has an impact on mood in bipolar patients who smoke marijuana Nonrandomized, prospective, comparative study (pilot study, with participants selected from a larger ongoing neuroimaging study)	Adults with bipolar disorder	Included if: • Smoked cannabis a minimum of 2,500 times in their lifetime • Used cannabis on at least 5 of the past 7 days • Tested positive for urinary cannabinoids • Diagnosis of cannabis abuse or dependence (DSM-5) • Diagnosis of bipolar I disorder (DSM-5) Excluded if: • More than 15 lifetime uses of any illicit drugs (amphetamines, opioids, phencyclidine, barbiturates, benzodiazepines, and cocaine) • Routinely had more than 15 drinks per week • Ever had a head injury or received electroconvulsive therapy	12	11	Mean age (SD): 24.3 years (4.3) cannabis use; 29.5 years (7.2) no cannabis use Sex not reported Race/ethnicity not reported Daily regimen that included 1 or more of the following drug classes (mood stabilizers, antidepressants, antipsychotics, and benzodiazepines): 92% cannabis use; 82% no cannabis use Mood stabilizers: 64% cannabis use; 75% no cannabis use Antidepressants: 36% cannabis use; 17% no cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Antipsychotics: 64% cannabis use; 50% no cannabis use Benzodiazepines: 18% cannabis use; 17% no cannabis use Mean age of cannabis use onset (SD): 16.7 years (2.6) cannabis use; NR, no cannabis use Mean age of bipolar disorder onset (SD): 14.9 years (2.9) cannabis use; 17.4 years (4.7) no cannabis use Mean smokes per week (SD): 13.7 (14.2) cannabis use Mean grams per week (SD): 4.6 (3.3) cannabis use Mean duration of use (SD): 7.6 (2.6) years, cannabis use Mean urinary THC (SD): 397 ng/ml (526)

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Kim et al., 2015[13] Community (public hospitals and private clinics) Australia Multi-site (Melbourne and Geelong) Moderate risk of bias	Regular cannabis use (defined as 3 times or more per week) over the past 3 months	No cannabis use (defined as less than 3 times per week) over the past 3 months	To assess the impact of cannabis use on the clinical course of patients with bipolar spectrum disorders, with a focus on long-term remission of mood symptoms according to gender and type of medication Nonrandomized, prospective study	Adults with bipolar spectrum disorders (bipolar 1 disorder or schizoaffective disorder)	Note. Details taken from The Bipolar Comprehensive Outcomes Study (BCOS): Baseline findings of an Australian cohort study (2008) Included if: • A primary diagnosis of bipolar I disorder (manic, mixed or depressed episode) or schizoaffective disorder as defined by the DSM of Mental Disorders, 4th Edition • At least 18 years of age • Prescription for at least 1 of the following mood stabilizers at baseline (as monotherapy or in combination) — olanzapine, lithium carbonate, sodium valproate or carbamazepine Excluded if: • Diagnosis of schizophrenia, organic psychosis or dementia • Involved in a controlled clinical trial 30 days prior to the study or at any time during the study	25	209	Mean age (SD): 32.3 years (7.6) cannabis use; 43.0 years (12.8) no cannabis use Mean age at onset (SD): 22.1 years (6.7) cannabis use; 22.9 years (9.9) no cannabis use Female: 9 of 25 (36.0%) cannabis use; 130 of 209 (62.2%) no cannabis use Race/ethnicity not reported Daily smoker: 22 of 25 (88.0%) cannabis use; 97 of 209 (46.4%) no cannabis use Alcohol dependence: 4 of 25 (16.0%) cannabis use; 36 of 209 (17.2%) no cannabis use Alcohol abuse: 4 of 25 (16.0%) cannabis use; 22 of 209 (10.5%) no cannabis use Bipolar disorder: 18 of 25 (72.0%) cannabis use; 154 of 209 (73.7%) no cannabis use Current psychotic feature: 6 of 25 (24.0%) cannabis use; 44 of 209 (21.1%) no cannabis use Use of olanzapine: 7 of 25 (28.0%) cannabis use; 76 of 209 (36.4%) no cannabis use Median baseline HAM-D score (IQR): 16 (10 to 25) cannabis use; 13 (7 to 18) no cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Median baseline YMRS score (IQR): 14 (4 to 24) cannabis use; 5 (2 to 11) no cannabis use Hospitalization in past 3 months: 7 of 25 (28.0%) cannabis use; 70 of 209 (33.5%) no cannabis use High suicide risk: 9 of 25 (36.0%) cannabis use; 42 of 209 (20.1%) no cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Kvitland et al., 2015[14] Community (inpatient and outpatient units) Norway Multi-site Moderate risk of bias	Continued cannabis use (defined as any cannabis use in the prior 6 months and use at follow-up)	No continued cannabis use (defined as no cannabis use or use only a 1 time point)	To evaluate the associations between course of illness in first treatment bipolar I disorder and continued cannabis use, from baseline to 1 year follow up Nonrandomized, prospective study	Adults with recent onset bipolar I disorder	Included if: • Meet DSM-IV diagnostic criteria for bipolar I disorder • Being within the first year of receiving adequate treatment for a manic episode • Age between 17 and 65 years Excluded if: • Pronounced cognitive deficits (IQ lower than 70) • Neurological disorder • Moderate or severe head injury	6	56	Mean age (SD): 30.5 years (9.7) continued cannabis use; 32.3 years (10.0) no continued cannabis use Female: 1 of 6 (16.7%) continued cannabis use; 36 of 56 (64.3%) no continued cannabis use Race/ethnicity not reported Mean IDS score (SD): 18.5 (11.9) continued cannabis use; 11.2 (10.0) no continued cannabis use Mean YMRS score (SD): 7.3 (5.5) continued cannabis use; 2.3 (4.0) no continued cannabis use Mean PANSS positive score (SD): 9.7 (2.6) continued cannabis use; 8.8 (2.6) no continued cannabis use Mean GAF-F score (SD): 49.0 (16.1) continued cannabis use; 65.3 (16.0) no continued cannabis use Current use of antipsychotic or mood stabilizing medication: 4 of 6 (66.7%) continued cannabis use; 42 of 56 (79.2%) no continued cannabis use

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
Sagar et al., 2016[15] Not clear US Not clear Moderate risk of bias	Cannabis - smoking only	No cannabis use	To determine the impact of marijuana on mood in bipolar patients and to examine whether marijuana confers an additional negative impact on cognitive function Nonrandomized, prospective, comparative study (pilot study, with participants selected from a larger study)	Adults with bipolar disorder	Included if: • Smoked cannabis a minimum of 2,500 times in their lifetime • Used cannabis on at least 4 of the past 7 days • Tested positive for urinary cannabinoids • Diagnosis of cannabis abuse or dependence (DSM-5) • Diagnosis of bipolar I disorder (DSM-5) • Refrained from use for 12 hours prior to a clinic visit Excluded if: • Any other axis I pathology • More than 15 lifetime uses of any illicit drugs (other than cannabis) • Non-medical use of prescription or over-the-counter medication • Neurological disorder or significant medical problems • Significant head injury with loss of consciousness • Received electroconvulsive therapy	12	18	Mean age (SD): 23.7 years (4.5) cannabis use; 28.6 years (6.7) no cannabis use Female: 1 of 12 (8.3%) cannabis use; 10 of 18 (55.5%) no cannabis use Race/ethnicity not reported Mean days of alcohol use per month (SD): 5.17 (4.71) cannabis use; 3.94 (5.71) no cannabis use Mood stabilizers: 75% cannabis use; 72% no cannabis use Antidepressants: 17% cannabis use; 28% no cannabis use Antipsychotics: 58% cannabis use; 56% no cannabis use Benzodiazepines: 8% cannabis use; 17% no cannabis use No medication: 8% cannabis use; 17% no cannabis use Mean age of cannabis use onset (SD): 16.9 years (2.6) cannabis use; NR, no cannabis use Mean age of bipolar disorder onset (SD): 15.2 years (3.2) cannabis use; 18.1 years (4.5) no cannabis use Mean smokes per week (SD): 15.5 (13.6)

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Mean grams per week (SD): 5.2 (2.8) Mean duration of use (SD): 6.8 years (2.8) Mean urinary THC (SD): 443 ng/ml (528)
Strakowski et al., 2007[16,18] Academic medical center US Single site Moderate risk of bias	Cannabis use disorder (assessed using the Addiction Severity Index, and meeting DSM-IV criteria for dependence)	No cannabis use disorder	To identify how the sequence of the onsets of a cannabis use disorder and bipolar disorder is associated with the subsequent course of each condition Nonrandomized, prospective, comparative study	People with bipolar I disorder (manic or mixed)	Included if: • Met DSM-IV criteria for bipolar disorder, manic or mixed (bipolar I disorder) • YMRS score greater than 20 • Consecutive admissions to hospital for mania between 1996 and 2003 • Age 12 to 45 years • No previous psychiatric hospitalizations • Less than 1 month of cumulative lifetime previous thymoleptic or antipsychotic drug exposure • Able to return for follow-up visits Excluded if: • Psychiatric symptoms were due entirely to acute medical illness or acute drug or alcohol withdrawal • Identified low IQ (< 70)	69 with cannabis use disorder	75 with no history of cannabis use disorder	Mean age (SD): 25 years (5) cannabis use disorder first; 19 years (6) bipolar disorder use first; 22 years (10) no cannabis use disorder Female: 11 of 33 (33%) cannabis use disorder first; 14 of 36 (39%) bipolar disorder use first; 44 of 75 (59%) no cannabis use disorder White: 24 of 33 (73%) cannabis use disorder first; 26 of 36 (72%) bipolar disorder use first; 51 of 75 (68%) no cannabis use disorder Cannabis use disorder, abuse: 9 of 33 (27%) cannabis use disorder first; 14 of 36 (39%) bipolar disorder use first Cannabis use disorder, dependence: 24 of 33 (73%) cannabis use disorder first; 22 of 36 (61%) bipolar disorder use first Mean cannabis use in prior month (SD): 12 days (13) cannabis use disorder first; 6 days (9) bipolar disorder use first; 1 day (4) no cannabis use disorder

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Mean age of cannabis use disorder onset (SD): 16 years (4) cannabis use disorder first; 18 years (5) bipolar disorder use first Alcohol use disorder, abuse: 5 of 33 (15%) cannabis use disorder first; 13 of 36 (36%) bipolar disorder use first; 8 of 75 (11%) no cannabis use disorder Alcohol use disorder, dependence: 18 of 33 (55%) cannabis use disorder first; 9 of 36 (25%) bipolar disorder use first; 8 of 75 (11%) no cannabis use disorder Mean alcohol intoxication in prior month (SD): 6 days (9) cannabis use disorder first; 3 days (7) bipolar disorder use first; 1 day (3) no cannabis use disorder Other drug use disorder: 8 of 33 (24%) cannabis use disorder first; 3 of 36 (8%) bipolar disorder use first; 0 no cannabis use disorder Mean education (SD): 12 years (2) cannabis use disorder first; 10 years (3) bipolar disorder use first; 11 years (4) no cannabis use disorder

Citation Setting Country Multi-Site or Single-Site Risk of Bias	Cannabis Use	Comparator	Study Aim Study Design	Population	Inclusion Criteria Exclusion Criteria	Number of Participants in the Cannabis Group	Number of Participants in the Comparator Group	Participant Characteristics
								Mixed state: 11 of 33 (33%) cannabis use disorder first; 20 of 36 (56%) bipolar disorder use first; 41 of 75 (55%) no cannabis use disorder Psychotic: 28 of 33 (85%) cannabis use disorder first; 26 of 36 (72%) bipolar disorder use first; 42 of 75 (56%) no cannabis use disorder Mean age of bipolar disease onset (SD): 23 years (6) cannabis use disorder first; 16 years (6) bipolar disorder use first; 18 years (10) no cannabis use disorder

Abbreviations. BDI: Beck Depression Inventory; CBD: cannabidiol; CBT: cognitive behavioral therapy; CCT: controlled clinical trial; CNS: central nervous system; CUD: cannabis use disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; GAF-F: Global Assessment Functioning scale; HAM-D: Hamilton Depression Rating Scale; IDS: Inventory of Depressive Symptoms; MDD: major depressive disorder; IQ: intelligence quotient; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions; NR: not reported; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; SD: standard deviation; THC: tetrahydrocannabinol; YMRS: Young Mania Rating Scale.

Table B2. Study Findings

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Anxiety disorders							
Gundugurti et al., 2024[35] Outpatient India Multi-site Moderate RoB RCT of CBD vs placebo for adults with mild to moderate GAD	Participants receiving CBD had significantly greater improvement in anxiety scores on all three scales: GAD-7: -7.02 (S.E: 0.25, 95% CI -7.52 to -6.52), P < .0001; HAM-A: -11.9 (S.E: 0.33, 95% CI -12.6 to -11.3), P < .0001; DASS-21: -7.72 (S.E: 0.28, 95% CI -8.27 to -7.17), P < .0001	Participants receiving CBD had significantly greater improvement in depression (PHQ-9: -6.77 [SE: 0.25, 95% CI -7.26 to -6.28], P < .0001)	Participants receiving CBD had significantly greater improvement in sleep quality (PSQI: -6.08 [SE: 0.21, 95% CI -6.50 to -5.66], P < .0001)	Participants receiving CBD had significantly greater improvement in global functioning and improvement (CGI-I: -2.31 [S.E: 0.07, 95% CI -2.44 to -2.18], P < .0001; CGI-S: -1.91 [SE: 0.08, 95% CI -2.06 to -1.75], P < .0001)	No concomitant medications known to have interaction with CBD	Not reported	There were no serious AEs. Participants in the CBD group reported more AEs than the placebo group (32% vs. 15%; P = nr). AEs included gastrointestinal symptoms, including nausea and upper abdominal pain, general pain or pyrexia, dizziness and headache, and almost all were mild.

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Bidwell et al., 2024[37] Participants recruited from the community US Single-site High RoB Quasi-experimental study of ad libitum use of THC dominant, THC: CBD balanced, or CBD dominant cannabis with a non-equivalent control group that did not use cannabis	PGIC: • all participants reported anxiety reductions over time • the 3 cannabis groups did not differ from each other • frequency of use was associated with greater perceived anxiety improvement DASS anxiety subscale: • At baseline, those with more frequent use had higher anxiety levels • all participants reported anxiety reductions over time • CBD dominant cannabis was associated with lower scores compared to THC-dominant use when accounting for frequency of use (difference = 1.03, SE = 0.45, p = .02) • There were no other group differences	DASS depression subscale: All participants experienced improvement over time, with no difference between groups	Not reported	Not reported	Psychotropic medication use excluded (anti-depressants and ADHD medications allowed)	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Fabre et al., 1978[6] Psychiatric clinic US Single site High risk of bias CCT of nabilone (1 mg 3 times a day) vs. placebo	Significant improvement with nabilone compared with placebo on the HAM-A overall ($P < .001$), the somatic anxiety factor ($P < .001$) and psychic anxiety ($P < .001$) On the 56-item symptom checklist, nabilone was associated with improvements on each factor (either significant or approaching significance); specifically, for anxiety ($P < .001$) and the overall score ($P < .002$) Patients reported dramatic improvement by day 3	On the 56-item symptom checklist, nabilone was associated with improvements on each factor (either significant or approaching significance); specifically, for depression ($P < .001$)	On the 56-item symptom checklist, nabilone was associated with improvements on each factor (either significant or approaching significance); specifically, for somatization ($P = .09$), interpersonal sensitivity ($P = .07$), and efficacy ($P = .002$)	Based on clinician and patient assessment, nabilone was associated with improvements when compared with placebo	Not reported	Not reported	Dry mouth: mild in 5 patients on 19 occasions, moderate in 9 patients on 28 occasions, and severe in 4 patients on 7 occasions Dry eyes: mild to moderate in 5 patients on 11 occasions Drowsiness: mild in 3 patients on 4 occasions, moderate in 3 patients on 7 occasions Headache: moderate to severe in 1 patient Insomnia: moderate to severe in 1 patient Other AEs reported were lump in the throat, nausea, tingling in the toes, red eyes, diarrhea, constipation, feeling slowed down In the placebo group, 1 patient reported mild nausea, 1 muscle weakness, and 1 vascular dilation around the eyes

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
							None reported (5 of 10 [50.0%] withdrew from the placebo arm because of lack of efficacy)

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Kwee et al., 2022[7,9] Mental health care centers The Netherlands Multi-site Moderate risk of bias RCT of CBD powder (300 mg) vs. placebo	No difference between groups for measures of anxiety at up to 6 months follow-up	No difference between groups for measures of depression at up to 6 months follow-up	No difference between groups in levels of fear avoidance at up to 6 months follow-up	Not reported	Not reported	Not reported	AEs: 2 isolated and 2 recurrent, CBD; 3 isolated and 3 recurrent, placebo; *P* = .40 Isolated AEs included dizziness and drowsiness in the CBD group and sweating, hot flushes, nausea, blurred vision, and a bad taste in the mouth, flu and gout attacks, and suicidal thoughts in the placebo group Recurrent AEs included tiredness and feeling of strong blood flow in the CBD group and tiredness, drowsiness, and headaches in the placebo group Suicidal thoughts occurred in 1 patient in the placebo group, leading to treatment discontinuation

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Masataka, 2019[8] Hospitals in the Osaka prefecture Japan Multi-site High risk of bias RCT of CBD oil (300 mg daily) vs. olive oil	Using the FNE, participants in the CBD group experienced a significant reduction in anxiety from baseline (24.4 vs. 19.1; *P* = .02); participants in the placebo group did not (23.5 vs. 23.3; *P* = .29) FNE scores were significantly lower in the CBD group post intervention (19.1 vs. 23.3; *P* = .002) Using the LSAS, participants in the CBD group experienced a significant reduction in anxiety from baseline (74.2 vs. 62.1; *P* = .03); participants in the placebo group did not (69.9 vs. 66.8; *P* = .42) LSAS scores were significantly lower in the CBD group post intervention (62.1 vs. 66.8; *P* = .002)	Not reported	Not reported	Not reported	At the end of treatment, participants in the CBD group were more likely to report they had decided to seek some form of treatment (medication and CBT) than participants in the placebo group (9 of 17 vs. 0 of 20; *P* < .001)	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Depressive disorders							
Feingold et al., 2017[10] Population US Multi-site Moderate risk of bias Prospective, national population survey of cannabis use	Not reported	Remission from MDD (defined as not meeting criteria of MDD diagnosis in the 12 months prior to Wave 2 among individuals who met the diagnostic criteria at Wave 1); 88.7% cannabis use without CUD; 76.8% cannabis use with CUD; 82.6% no cannabis use (P = .19 for cannabis use without CUD and P = .08 for cannabis use with CUD, when compared with no cannabis use) When compared with people with MDD who did not use cannabis, people with MDD who used cannabis but did not have CUD had no statistically significant differences in: • Depressed mood most of the day, nearly every day • Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day	Not reported	Not reported		After adjusting for baseline confounding factors, no associations were found between cannabis use and suicidality, functionality and quality of life Considering measures associated with suicidality at baseline, though people who used cannabis and individuals with CUD differed significantly from people who did not use cannabis in prevalence rates of having thoughts about committing suicide, these findings did not retain significance after adjusting for baseline confounding factors	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
		• Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day • Insomnia or hypersomnia nearly every day Psychomotor agitation or retardation nearly every day • Fatigue or loss of energy nearly every day • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day • Diminished ability to think or concentrate, or indecisiveness, nearly every day • 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				After controlling for baseline confounders people who used cannabis and individuals with CUD were not significantly more prone to report being fired from work, having trouble with boss or coworker, getting divorced or separated, or quitting school more than once at follow-up compared to people who did not use cannabis No differences were found in rates of treatment utilization among people who used cannabis and individuals with CUD compared to people who did not use cannabis No significant differences were found between people who used cannabis and people who did not use cannabis in baseline QoL scores, and no significant association was found between level of cannabis use and QoL scores at follow-up	

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
		When compared with people with MDD who did not use cannabis, people with MDD who used cannabis and who also had CUD were significantly more likely to experience: • Depressed mood most of the day, nearly every day (ORs ranged from 1.50 to 1.77; $P \leq .04$, but was nonsignificant when fully adjusted for baseline suicidality, sociodemographic factors, psychiatric disorders and substance use disorder) • Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (ORs ranged from 2.35 to 2.85; $P \leq .005$ for all models) • Psychomotor agitation or retardation nearly every day (ORs ranged from 2.94 to 3.72; $P < .001$ for all models)					

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
		• Fatigue or loss of energy nearly every day (ORs ranged from 2.03 to 2.31; *P* ≤ .02 for all models) • Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day (ORs ranged from 2.30 to 2.87; *P* ≤ .004 for all models) • Insomnia or hypersomnia nearly every day (ORs ranged from 2.30 to 2.62; *P* ≤ .005 for all models) • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (ORs ranged from 2.30 to 2.92; *P* ≤ .04 for all models) • Diminished ability to think or concentrate, or indecisiveness, nearly every day (ORs ranged from 2.09 to 2.29; *P* ≤ .01 for all models)					

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
		• 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 (ORs ranged from 1.78 to 2.59; $P \leq .003$, but was nonsignificant when full adjusted for baseline suicidality, sociodemographic factors, psychiatric disorders and substance use disorder)					
Bipolar disorders							
Pinto et al., 2024[36] Outpatient Brazil Single site Moderate RoB Participants with bipolar I or bipolar II disorder experiencing a current major depressive episode were randomized to CBD or placebo	There was no difference between groups in anxiety (HAM-A difference: -0.51 (95% CI, -5.55 to 4.54), P = 0.84)	MADRS scores at week 8: no difference between CBD and placebo (-0.82 [95% CI, -7.81 to 6.17], P = 0.82 Exploratory analysis (n =11): increased dose of CBD due to lack of early response had significant improvements in depression from week 2-8 compared to placebo.	Response rate: no difference between groups (CBD 57.9%, Placebo 62.5%, P = 1.0) Remission rate: no difference between groups (CBD 47.4%, Placebo 31.3%, P = 0.49). Psychopathology: no difference in BPRS. Difference: -3.24 (95% CI, -7.45 to 0.97), P = 0.13	Functioning: No difference CGI-Severity Difference: 0.52 (95% CI, -0.59 to 1.63), P = 0.36 FAST Difference: 0.52 (95% CI, -10.1 to 11.2), P = 0.92	Regular use of lithium, valproate, or atypical antipsychotics at therapeutic levels for at least 4 weeks before baseline assessment	Not reported	No differences between CBD and placebo in YMRS, CGI-S mania, and UKU scores

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Baethge et al., 2008[11] Single hospital (international research center) US Single site Moderate risk of bias Nonrandomized, prospective, longitudinal study of cannabis use	Not reported	Depression was unrelated to cannabis use in preceding, the same, or following quarters (excess risk ranged from 0.9% to 1.9%; *P* values ranged from .61 to .83)	Cannabis use in the preceding quarter was associated with a 11.1% increase in the risk of mania or hypomanic morbidity (95% CI, 5.4% to 16.8%; *P* < .001) Cannabis use in the same quarter was associated with a 11.6% increase in the risk of mania or hypomanic morbidity (95% CI, 5.3% to 17.8%; *P* < .001) No association between cannabis use and mania or hypomanic morbidity in the following quarter (excess risk, 1.7%; 95% CI, 0.3% to 3.7%; *P* = .10)	Not reported	Not reported	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
EMBLEM[17,19-21] Community (inpatient and outpatient units) Europe (14 countries) Multi-site Moderate risk of bias Nonrandomized, prospective study	Not reported	No significant association was found between any cannabis use and CGI-BP depression scores (at 12 months, 1.70 vs. 1.70; $P \geq .05$)[17] No significant association between cannabis use or dependence and switching from manic or mixed episode of bipolar disorder to depression[20] More people had suicide attempts in the cannabis use group compared with the never use and previous use groups (6.9% vs. 3.0% and 4.4%; $P = .046$)[21]	People with bipolar disease who used cannabis had significantly higher CGI-BP mania scores than people who did not use cannabis (at 12 months, 2.0 vs, 1.9; $P = .001$ over the 12 months)[17] People with bipolar disease who used cannabis had significantly higher CGI-BP hallucination/ delusion scores than people who did not use cannabis (at 12 months, 1.6 vs. 1.4; $P = .006$ over the 12 months)[17] People with bipolar disease who also used cannabis were significantly less likely to achieve recovery than people who had never used cannabis or had used in the past (18.9% vs. 31.8% and 38.7%; $P = .003$)[21] People with bipolar disease who also used cannabis were significantly less likely to achieve remission than people who had never used cannabis	People with bipolar disease who used cannabis had significantly higher CGI-BP overall illness scores than people who did not use cannabis (at 12 months, 2.4 vs. 2.3; $P = .004$ over the 12 months)[17] People with bipolar disease who also used cannabis were significantly more likely to experience some work impairment than people who had never used cannabis or had used in the past (73.1% vs. 61.4% and 53.5%; $P = .008$)[21] No significant association between cannabis use and independent residence (70.5% vs. 63.5% and 60.7%; $P = .23$)[21]	Lower treatment compliance: OR, 1.38; 95% CI, 1.12 to 1.72; $P = .003$[17] However, when other substance use was included, the relationship was no longer significant[17]	People with bipolar disease who used cannabis were significantly more likely to not have a relationship over the 12 months (OR, 1.64; 95% CI, 1.13 to 2.38; $P = .009$ over the 12 months)[17] People with bipolar disease who used cannabis were significantly less likely to engage in no social activities (at 12 months, 5.1% vs. 9.1%; $P = .02$ over the 12 months); however, when age, age of onset, and alcohol abuse were included, the relationship was no longer statistically significant[17] People with bipolar disease who used cannabis were significantly more likely to report being dissatisfied with their life (at 12 months, 22.4% vs. 14.3%; $P = .007$ over the 12 months)[17]	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
			or had used in the past (42.6% vs. 61.9% and 68.1%; *P* < .001)[21] People with bipolar disease who also used cannabis were significantly more likely to experience recurrence than people who had never used cannabis or had used in the past (60.3% vs. 47.3% and 42.1%; *P* = .01)[21] People with bipolar disease who also used cannabis were significantly more likely to experience relapse than people who had never used cannabis or had used in the past (46.3% vs. 34.9% and 29.8%; *P* = .02).[21] From logistic models, current cannabis use vs. no use was significantly associated with lower levels of recovery (OR, 0.39; 95% CI, 0.21 to 0.73), lower levels of remission (OR, 0.57; 95% CI, 0.37 to 0.89), higher levels of recurrence (OR, 1.69; 95% CI, 1.11 to 2.58), greater work	People with bipolar disease who also used cannabis were significantly more likely to live apart from their partner than people who had never used cannabis or had used in the past (75.0% vs. 53.3% and 67.4%; *P* < .001)[21]		There was no significant association between any cannabis use and independent living, the number of dependents to care for and the extent of work impairment over 12 months.[17]	

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
			impairment (OR, 1.85; 95% CI, 1.12 to 3.04), and not living with a partner (OR, 2.91; 1.37 to 6.17).[21] No significant association between current use and relapse or independent residence.[21] When adjusted for alcohol and other substance use, only recurrence (OR, 1.59; 95% CI, 1.01 to 2.52) and not living with a partner (OR, 3.41; 95% CI, 1.47 to 7.90) remained significant.[21] No significant association between prior use and any outcomes of interest.[21] Time to recovery, recurrence, and relapse were significantly associated with cannabis use; however, when other substance use (including alcohol) was added, only recurrence remained significant.[21]				

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Gruber et al., 2012[12] Community US Multi-site High risk of bias Nonrandomized, prospective, comparative study of cannabis use	Note. Reported scores post-smoking. Overall, while the cannabis use group reported generally worse mood ratings than the no cannabis group prior to smoking cannabis, they demonstrated improvement on several scales post-cannabis use as compared to people with no cannabis use Mean TMD score over 4 weeks: 12.22 (21.32) cannabis use; 20.60 (26.19) no cannabis use; *P* = .002 Mean HAM-A score over 4 weeks: 3.83 (4.29) cannabis use; 4.62 (4.82) no cannabis use; *P* > .05	Mean MADRS score over 4 weeks: 11.73 (8.27) cannabis use; 6.65 (6.32) no cannabis use; *P* ≤ .05	Mean YMRS score over 4 weeks: 5.38 (4.37) cannabis use; 3.70 (4.41) no cannabis use; *P* ≤ .05 Mean POMS - vigor score over 4 weeks: 10.99 (4.86) cannabis use; 10.35 (6.05) no cannabis use; *P* > .05 Mean POMS - anger score over 4 weeks: 3.50 (5.44) cannabis use; 3.85 (4.96) no cannabis use; *P* > .05 Mean POMS - confusion score over 4 weeks: 4.94 (3.26) cannabis use; 7.41 (4.20) no cannabis use; *P* < .001 Mean POMS - tension score over 4 weeks: 3.70 (4.21) cannabis use; 6.58 (4.96) no cannabis use; *P* < .001 Mean POMS - fatigue score over 4 weeks: 5.30 (4.82) cannabis use; 6.96 (5.69) no cannabis use; *P* = .005 Mean POMS - depression score over 4 weeks: 5.76 (7.28) cannabis use; 6.15 (7.08) no cannabis use; *P* > .05	Not reported	Not reported	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Kim et al., 2015[13] Community (public hospitals and private clinics) Australia Multi-site (Melbourne and Geelong) Moderate risk of bias Nonrandomized, prospective study of cannabis use	Not reported	Median remission from depression (defined as HAM-D score of ≤ 8; IQR): 22 (0 to 44) cannabis use; 33 (11 to 67) no cannabis use; *P* = .04 Females who used cannabis were significantly less likely to achieve remission than females who did not use cannabis (median, 0 vs. 33; *P* = .002) No difference in median remission between groups for males (median, 39 vs. 3; *P* = .60) People on a mood stabilizer alone who used cannabis were marginally less likely to achieve remission than people on a mood stabilizer alone who did not use cannabis (median, 17 vs. 33; *P* = .05) No difference in remission between groups for people on olanzapine with or without a mood stabilizer (median, 22 vs. 33; *P* = .38)	Median total remission (defined as remission of both mania and depression; IQR): 11 (0 to 39) cannabis use; 33 (11 to 67) no cannabis use; *P* = .03 Females who used cannabis were significantly less likely to achieve total remission than females who did not use cannabis (median, 0 vs. 33; *P* = .005) No difference in remission between groups for males (median, 28 vs. 33; *P* = .45) People on a mood stabilizer alone who used cannabis were significantly less likely to achieve total remission than people on a mood stabilizer alone who did not use cannabis (median, 11 vs. 33; *P* = .03) No difference in remission between groups for people on olanzapine with or without a mood stabilizer (median, 22 vs. 33; *P* = .47)	Not reported	Not reported	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
			Median remission from mania (defined as YMRS score of ≤ 12; IQR): 78 (44 to 94) cannabis use; 89 (67 to 100) no cannabis use; *P* = .05 No difference in remission between groups for females (median, 89 vs. 89; *P* = .80) Males who used cannabis were significantly less likely to achieve remission than males who did not use cannabis (median, 78 vs. 89; *P* = .02) No difference in remission between groups for people on a mood stabilizer alone (median, 83 vs. 89; *P* = .37) People on olanzapine with or without a mood stabilizer and who used cannabis were significantly less likely to achieve remission than people on olanzapine with or without a mood stabilizer who did not use cannabis (median, 78 vs. 89; *P* = .03)				

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Kvitland et al., 2015[14] Community (inpatient and outpatient units) Norway Multi-site Moderate risk of bias Nonrandomized, prospective study of cannabis use	Not reported	Not reported	Continued use of cannabis was significantly associated with elevated mood, measured using the YMRS, at 1 year (7.33 continued cannabis use; 2.25 no continued cannabis use; *P* = .005) A similar association was seen when assessed in multiple regression analyses No difference between groups for depression (IDS, 18.50 continued cannabis use; 11.17 no continued cannabis use; *P* = .10) or for psychosis (PANSS-P, 9.67 continued cannabis use; 8.70 no continued cannabis use; *P* = .38)	Continued use of cannabis was significantly associated with worse global functioning, measured using the GAF-F, at 1 year (49.0 continued cannabis use; 66.0 no continued cannabis use; *P* = .013) Elevated mood mediated the effect of cannabis use on global functioning	Not reported	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Sagar et al., 2016[15] Not clear US Not clear Moderate risk of bias Nonrandomized, prospective study of cannabis use	Note. Reported scores post-smoking. Overall, while the cannabis use group reported generally higher depression and a tendency for higher mania scores than the no cannabis group prior to smoking cannabis, they demonstrated improvement on cannabis use, resulting in similar levels to those of people with no cannabis use Mean TMD score over 4 weeks: 11.15 (13.69) cannabis use; 22.53 (21.17) no cannabis use; *P* = .24 Mean HAM-A score over 4 weeks: 4.23 (4.12) cannabis use; 4.43 (3.44) no cannabis use; *P* = .40	Mean MADRS score over 4 weeks: 9.35 (6.89) cannabis use; 7.21 (5.43) no cannabis use; *P* = .13	Mean YMRS score over 4 weeks: 5.61 (3.81) cannabis use; 3.99 (3.23) no cannabis use; *P* = .15 Mean POMS - vigor score over 4 weeks: 10.78 (3.52) cannabis use; 9.71 (3.67) no cannabis use; *P* = .38 Mean POMS - anger score over 4 weeks: 2.35 (2.54) cannabis use; 4.24 (3.41) no cannabis use; *P* = .17 Mean POMS - confusion score over 4 weeks: 5.85 (3.11) cannabis use; 7.06 (3.39) no cannabis use; *P* = .44 Mean POMS - tension score over 4 weeks: 4.15 (2.62) cannabis use; 6.92 (3.37) no cannabis use; *P* = .07 Mean POMS - fatigue score over 4 weeks: 4.88 (3.24) cannabis use; 7.06 (3.48) no cannabis use; *P* = .26 Mean POMS - depression score over 4 weeks: 4.69 (3.64) cannabis use; 6.95 (7.04) no cannabis use; *P* = .43	Not reported	Not reported	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
Strakowski et al., 2007[16,18] Academic medical center US Single site Moderate risk of bias Nonrandomized, prospective study of cannabis use	Not reported	Not reported	People who developed cannabis use disorder before bipolar disorder were significantly more likely to achieve affective symptom recovery than people who developed bipolar disorder before cannabis use disorder, or who did not have cannabis use disorder (P = .003). There was no significant difference in recovery between people who developed bipolar disorder before cannabis use disorder and those who did not have cannabis use disorder (P = .76) However, when adjusted for age, sex, education, presence of psychosis, age at bipolar disorder onset, and history of an alcohol or other drug use disorder at the index assessment, the differences in time to recovery were no longer statistically significant (P = .33)	Not reported	No difference between groups in full adherence with at least 1 mood stabilizer (56% vs. 42% vs. 56%; $P \geq .05$) No difference between groups in the use of lithium, anticonvulsants, atypical antipsychotics, or antidepressants; however, significantly greater use of conventional antipsychotics in the comorbid groups (24% vs. 22% vs. 7%; P = .02)	Not reported	Not reported

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
			There was no difference between groups for recurrence of affective episodes (*P* = .16) or time to recurrence (*P* = .91) No difference between groups in percentage of weeks in recovery (*P* = .11), weeks with subdromal affective symptoms (*P* = .62) People who developed bipolar disorder before cannabis use disorder had significantly longer time in an affective episode than people who developed bipolar disorder before cannabis use disorder, or who did not have cannabis use disorder (*P* = .004), especially in manic (*P* = .06) and mixed (*P* = .03) episodes when compared with no cannabis use disorder				

Citation Setting Country Multi-Site or Single-Site Risk of Bias Study Summary	Anxiety	Depression	Other Symptoms Related to the Primary Diagnosis	Global Measures of Functioning or Improvement	Use of Other Medications for Primary Condition or Symptoms	Quality of Life or Other Measures of Functioning	AEs and SAEs, Including Withdrawals Due to AEs
			Patients in both comorbid groups experienced significantly more rapid cycling than patients without cannabis use disorder (12% vs. 19% vs. 5%; *P* = .04)				

Abbreviations. AE: adverse event; BMI: Body Mass Index; BPRS: Brief Psychiatric Rating Scale; CBD: cannabidiol; CBT: cognitive behavioral therapy; CGI-BP: Clinical Global Impression-Bipolar; CGI-S: Clinical Global Impression-Severity; CI: confidence interval; CCT: controlled-clinical trial; CUD: cannabis use disorder; DASS: Depression Anxiety Stress Scale; FAST: Functioning Assessment Short Test; FNE: Fear of Negative Evaluation Questionnaire; GAD: generalized anxiety disorder; GAF-F: Global Assessment Functioning scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; IDS: Inventory of Depressive Symptoms; IQR: interquartile range; LSAS: Liebowitz Social Anxiety Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; OR: odds ratio; PANSS-P: Positive and Negative Syndrome Scale-Psychotic; PGIC: Patient Global Impression of Change Scale; PHQ-9: Patient Health Questionnaire-9; POMS: Profile of Mood States; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event; THC: tetrahydrocannabinol; TMD: total mood disturbance; UKU: Udvalg for Kliniske Undersøgelser; YMRS: Young Mania Rating Scale.

Table B3. Risk of Bias for Randomized Controlled Trials

Citation	1. Randomization	2. Allocation	3. Blinding	4. FU	5. Outcome	6. Analysis	7. Summary estimate	8. Baseline	9. Loss to FU	10. Author Interests	11. Funding	12. Applicability	Overall RoB
Gundugurti et al., 2024	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Kwee et al., 2022[7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Moderate
Masataka, 2019[8]	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Unclear	Yes	No	Yes	Yes	High
Pinto et al., 2024[36]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Moderate

Abbreviations. FU: follow-up; RoB: risk of bias.

1. *An appropriate method of randomization is used to allocate participants or clusters to groups, such as a computer random number generator.*
2. *An adequate allocation sequence concealment method is used to prevent investigators and participants from influencing enrolment or intervention allocation.*
3. *Investigators, outcome assessors, and participants are unaware (blinded or masked) of intervention status.*
4. *The trial has an appropriate length of follow-up and groups are assessed at the same time points.*
5. *Investigators use single outcome measures and do not rely on just composite outcomes (i.e., a combination of outcomes in a single measure).*
6. *Participants are analyzed based on random assignment (intention-to-treat analysis).*
7. *The most appropriate summary estimate (e.g. risk ratio, hazard ratio, odds ratio) is used.*
8. *Baseline characteristics between groups or clusters are similar.*
9. *Losses to follow-up are unlikely to significantly bias the results (i.e., losses are non-differential and less than 20% of the randomized sample).*
10. *Disclosures of interest are provided for authors, funders, and commissioners of the study and are unlikely to have a significant impact on study validity.*
11. *There is a description of source(s) of funding and funding is unlikely to have a significant impact on study validity.*
12. *The results of this study are directly applicable to the intended purpose of the report.*

Table B4. Risk of Bias for Quasi-Experimental Studies

Citation	1. Control	2. Inclusion	3. Population	4. Measures	5. Timing	6. Assessors	7. Contamination	8. Length of FU	9. FU equal	10. Confounders	11. Author Interests	12. Funding	13. Applicability	Overall RoB
Bidwell et al, 2024	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes	High
Fabre et al, 1978[6]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Yes	No	No	No	Yes	High

Abbreviations. FU: follow-up; RoB: risk of bias.

1. *The study design has a control group (If NO, the risk of bias is rated as high).*
2. *The inclusion and exclusion criteria are the same across the intervention and comparison group(s).*
3. *Participant characteristics are balanced between groups or matched groups (e.g., propensity scores).*
4. *Multiple pre- and post-intervention outcomes were measured.*
5. *Pre- and post-intervention outcomes were measured concurrently among intervention and control groups.*
6. *The assessor could not influence the outcome, exposure, or intervention status of the participants.*
7. *The study was designed to reduce the possibility that control participants were exposed to the intervention (contamination bias).*
8. *The length of follow-up was sufficient and appropriate for all outcomes.*
9. *All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).*
10. *The study attempts appropriate sensitivity analysis or other statistical adjustment related to confounders, inclusion/exclusion criteria, losses to follow-up, missing data, or adherence to intervention, as needed.*
11. *Disclosures of interest are provided for authors/funders/commissioners of the study and are unlikely to have a significant impact on study validity.*
12. *There is a description of source(s) of funding and funding is unlikely to have a significant impact on study validity.*
13. *The results of this study are directly applicable to the intended purpose of the report.*

Table B5. Risk of Bias for Nonrandomized Studies

Citation	1. Population	2. Assessment	3. Outcome	4. Blinding	5. FU	6. Length of FU	7. Loss to FU	8. Analysis	9. Confounders	10. Effect Size	11. Loss to FU by Group	12. Author Interests	13. Funding	14. Applicability	Overall RoB
Baethge et al., 2003[11]	Yes	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	No	Yes	Yes	Moderate
EMBLEM 2009[17]	Yes	Yes	Unclear	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Yes	Moderate
Feingold et al., 2017[10]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Moderate
Gruber et al, 2012[12]	Yes	Yes	Yes	No	Yes	Yes	Unclear	Unclear	No	Yes	Yes	No	Yes	Yes	High
Kim et al., 2015[13]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Moderate
Kvitland et al., 2015[14]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate
Sagar et al., 2016[15]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Moderate
Strakowski et al., 2007[16]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate

Abbreviations. FU: follow-up; RoB: risk of bias.

1. *The exposed and unexposed groups being studied are selected from a source population that is comparable in all respects other than the exposure under investigation.*
2. *The measure of assessment of exposure is valid, reliable, and consistently assessed across all study participants.*
3. *The outcome measure is valid, reliable, and consistently assessed across all study participants.*
4. *Outcome assessors are blind to the exposure status of participants or where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the outcome assessment.*
5. *The study has an appropriate length of follow-up to observe an association between the exposure and outcome, if it existed.*
6. *Exposure groups are followed for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).*
7. *Comparison, by exposure status, is made between those retained in the study and those who dropped out or were lost to follow up.*
8. *A clearly defined and appropriate process for inclusion of confounding variables in analyses is done.*
9. *Main confounders are collected and adjusted for in analyses.*
10. *The most appropriate effect size (e.g., risk ratio) is used.*
11. *Lost to follow-up is unlikely to significantly bias the results (i.e., non-differential and less than 20% of sample from baseline).*
12. *Disclosures of interest are provided for authors, funders, and commissioners of the study and are unlikely to have a significant impact on study validity.*
13. *There is a description of source(s) of funding and funding is unlikely to have a significant impact on study validity.*
14. *The results of this study are directly applicable to the intended purpose of the report.*

Appendix C. Bibliography of Included Studies

*Primary publication

*Baethge C, Hennen J, Khalsa HM, Salvatore P, Tohen M, Baldessarini RJ. Sequencing of substance use and affective morbidity in 166 first-episode bipolar I disorder patients. *Bipolar Disord.* 2008;10(6):738-741. Doi: 10.1111/j.1399-5618.2007.00575.x.

*Bidwell LC, Martin-Willett R, Skrzynski C, et al. Acute and extended anxiolytic effects of cannabidiol in cannabis flower: a quasi-experimental ad libitum use study. *Cannabis Cannabinoid Res*. 2024;22:22. doi: 10.1089/can.2023.0187.*Fabre LF, McLendon DM, Stark P. Nabilone, a cannabinoid, in the treatment of anxiety: an open-label and double-blind study. *Current Therapeutic Research.* 1978;24(2):161-169.

*Feingold D, Rehm J, Lev-Ran S. Cannabis use and the course and outcome of major depressive disorder: A population based longitudinal study. *Psychiatry Res.* 2017;251:225-234. Doi: 10.1016/j.psychres.2017.02.027.

*Gundugurti PR, Banda N, Yadlapalli SSR, et al. Evaluation of the efficacy, safety, and pharmacokinetics of nanodispersible cannabidiol oral solution (150 mg/mL) versus placebo in mild to moderate anxiety subjects: A double blind multicenter randomized clinical trial. *Asian J Psychiatr*. 2024;97:104073. doi: 10.1016/j.ajp.2024.104073.

*Gruber SA, Sagar KA, Dahlgren MK, Olson DP, Centorrino F, Lukas SE. Marijuana impacts mood in bipolar disorder: a pilot study. *Ment Health Subst Use.* 2012;5(3):228-239. Doi: 10.1080/17523281.2012.659751.

Haro JM, van Os J, Vieta E, et al. Evidence for three distinct classes of 'typical', 'psychotic' and 'dual' mania: results from the EMBLEM study. *Acta Psychiatr Scand.* 2006;113(2):112-120. Doi: 10.1111/j.1600-0447.2005.00692.x.

*Kim SW, Dodd S, Berk L, et al. Impact of Cannabis Use on Long-Term Remission in Bipolar I and Schizoaffective Disorder. *Psychiatry Investig.* 2015;12(3):349-355. Doi: 10.4306/pi.2015.12.3.349.

*Kvitland LR, Melle I, Aminoff SR, et al. Continued cannabis use at one year follow up is associated with elevated mood and lower global functioning in bipolar I disorder. *BMC Psychiatry.* 2015;15:11. Doi: 10.1186/s12888-015-0389-x.

*Kwee CM, Baas JM, van der Flier FE, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: A randomised controlled trial. *Eur Neuropsychopharmacol.* 2022;59:58-67. Doi: 10.1016/j.euroneuro.2022.04.003.

*Masataka N. Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers with Social Anxiety Disorders. *Front Psychol.* 2019;10:2466. Doi: 10.3389/fpsyg.2019.02466.

*Pinto JV, Crippa JAS, Cereser KM, et al. Cannabidiol as an adjunctive treatment for acute bipolar depression: a pilot study: le cannabidiol comme traitement d'appoint de la depression bipolaire aigue: une etude pilote. *Can J Psychiatry*. 2024;69(4):242-251. doi: 10.1177/07067437231209650.

*Sagar KA, Dahlgren MK, Racine MT, Dreman MW, Olson DP, Gruber SA. Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood. *PloS One.* 2016;11(6):e0157060. Doi: 10.1371/journal.pone.0157060.

*Strakowski SM, DelBello MP, Fleck DE, et al. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch Gen Psychiatry.* 2007;64(1):57-64. Doi: 10.1001/archpsyc.64.1.57.

Strakowski SM, DelBello MP, Fleck DE, Arndt S. The impact of substance abuse on the course of bipolar disorder. *Biol Psychiatry.* 2000;48(6):477-485. Doi: 10.1016/s0006-3223(00)00900-8.

Van der Flier FE, Kwee CMB, Cath DC, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: study protocol of a randomized controlled trial. *BMC Psychiatry.* 2019;19(1):69. Doi: 10.1186/s12888-019-2022-x.

*van Rossum I, Boomsma M, Tenback D, Reed C, van Os J, Board EA. Does cannabis use affect treatment outcome in bipolar disorder? A longitudinal analysis. *J Nerv Ment Dis.* 2009;197(1):35-40. Doi: 10.1097/NMD.0b013e31819292a6.

Vieta E, Angst J, Reed C, Bertsch J, Haro JM, board Ea. Predictors of switching from mania to depression in a large observational study across Europe (EMBLEM). *J Affect Disord.* 2009;118(1-3):118-123. Doi: 10.1016/j.jad.2009.02.007.

Zorrilla I, Aguado J, Haro JM, et al. Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? *Acta Psychiatr Scand.* 2015;131(2):100-110. Doi: 10.1111/acps.12366.