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Original article



Cannabis and cannabinoids for the treatment of mental and substance use disorders and symptoms: A systematic review and meta-analysis of experimental and observational studies

Chrianna Bharat [a,b,*], Xintong Huang [a], Gabrielle Campbell [a,c], Calvert Tisdale [a,d], Sophia Glasgow [c], Suzanne Nielsen [d], Zoe Pollock [a], Thomas Santo Jr [a], Swara Kale [a], Michael Farrell [a], Louisa Degenhardt [a]

[a] National Drug and Alcohol Research Centre, UNSW Sydney, Randwick, Australia
[b] School of Population and Global Health, University of Western Australia, Perth, Australia
[c] National Centre for Youth Substance Use Research (NCYSUR), School of Psychology, University of Queensland, Brisbane, Australia
[d] Monash Addiction Research Centre, Eastern Health Clinical School, Monash University, Melbourne, Australia

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ABSTRACT

Background: Interest in cannabinoids for mental and substance use disorders is increasing. We examined experimental and observational evidence for treating these disorders and their symptoms.
Methods: Systematic review and meta-analysis (PROSPERO CRD42023467536). We searched CENTRAL, MEDLINE, Embase and PsycINFO to May 2025 for studies of cannabinoids in adults (≥18 years) with ADHD, anxiety, depression, PTSD, psychosis or Tourette syndrome, or alcohol, cannabis, opioid or tobacco use disorders. Two reviewers screened, extracted and assessed quality using a risk-of-bias tool and GRADE.
Results: We included 82 experimental and 118 observational studies. In RCTs, cannabinoids reduced anxiety symptoms (SMD=−0.40; 95% CI: −0.57, −0.23; I^2=90%) and, in one small trial, PTSD symptoms (SMD=−2.60; 95% CI: −4.58, −0.62; n=20), with trivial-to-no effect on depression (SMD=−0.20; 95% CI: −0.43, 0.04; I^2=91.6%), ADHD, psychosis and Tourette syndrome. Much anxiety and depression evidence came from symptoms measured as secondary outcomes in other primary conditions. Cannabinoids worsened cannabis use disorder severity in one RCT (SMD=2.35; 95% CI: 1.49, 3.21), with no effect on craving or withdrawal; evidence for alcohol, opioid and tobacco use disorders was very limited. Observational studies suggested improvements but had high risk of bias. The only significant safety finding was increased withdrawals due to adverse events with THC (OR=2.78; 95% CI: 1.66, 4.65). Certainty was predominantly very low.
Discussion: The evidence base shows very low certainty, high heterogeneity and methodological limitations, and is insufficient to support cannabinoids as first-line treatment. Signals for anxiety and PTSD are limited by indirectness and low certainty; no benefit was evident for depression; THC-related safety signals warrant careful consideration.

1. Introduction

The use of cannabinoids for medicinal purposes has expanded rapidly worldwide, with an increasing number of countries introducing legislation that allows legal access to medicinal cannabinoid products (Compton et al., 2017). Beyond pain management, medicinal cannabinoids have primarily been used for symptoms of mental disorders (Kosiba et al., 2019), and increasing reports suggest they are used for the management of substance use disorders (Compton et al., 2017). Despite this, previous reviews examining the use of cannabinoids for mental and substance use disorders have concluded that the evidence base for their effectiveness is limited (Hsu et al., 2025; Black et al., 2019).

Given the increasing use of medicinal cannabinoids, there is an ongoing need to systematically review the rapidly evolving evidence base. We have therefore updated our previous review, conducted in 2019, of the efficacy, effectiveness and safety of medicinal cannabinoids

* Corresponding author.
E-mail address: c.bharat@unsw.edu.au (C. Bharat).

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on mental disorders, and expanded previous reviews of medicinal cannabinoids (Black et al., 2019; Hansen et al., 2023; Spiga et al., 2025; Nielsen et al., 2019) to consider substance use disorders.

We aimed to examine the available evidence for all types of medicinal cannabinoids and study designs (experimental and observational) to ascertain the impact of medicinal cannabinoids on the symptoms and remission of mental (anxiety, attention-deficit hyperactivity disorder (ADHD), depression, psychosis, post-traumatic stress disorder (PTSD) and Tourette syndrome) and substance use disorders (SUD), including cannabis use disorder (CUD), alcohol use disorder (AUD), tobacco use disorder (TUD), and opioid use disorder (OUD). Additionally, we examined the safety of medicinal cannabinoids among populations with mental disorders or SUD, including all-cause, serious, and treatment-related adverse events, all-cause withdrawals, and withdrawals due to adverse events in experimental studies.

2. Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidance (Prasad, 2024; Page et al., 2021). This meta-analysis was registered in PROSPERO (CRD42023467536).

2.1. Search strategy

We systematically searched MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL), accessed via Ovid. Searches were restricted to human studies with no language limits applied.

For the mental health conditions originally reported in Black et al. (2019) (Black et al., 2019), we updated searches to include publications from May 2018 to May 2025. We modified the search strategy by replacing specific study type terms (e.g., 'prospective study', 'clinical trials', 'randomised controlled trial') with four explode terms: 'treatment', 'therapeutic', 'therapy', and 'intervention'. This modification broadened the search scope and reduced the likelihood of missing relevant studies.

For cannabis use disorder, we updated the search originally conducted by Nielsen et al. (2019) (Nielsen et al., 2019). As the original review covered experimental studies (e.g., clinical trials, randomised controlled trials) up to March 2018, we searched for experimental studies published between January 2018 and May 2025. To capture observational studies, we conducted an additional search for observational studies published between 1980 and May 2025. For the remaining substance use disorders (alcohol, opioid and tobacco), we conducted new searches covering the full timeframe from database inception to May 2025. Full search strategies are included in **Appendix A**.

We supplemented database searches using several methods. First, we applied a snowballing approach by handsearching and reviewing reference lists of included systematic reviews to identify additional relevant work. Second, we searched for peer-reviewed publications of ongoing trials using trial registration numbers and titles. Third, we searched for full peer-reviewed publications of studies initially published only as conference abstracts. All identified studies were deduplicated in EndNote then uploaded into Covidence for screening.

2.2. Inclusion and exclusion criteria

The review included experimental (randomised and nonrandomised controlled trials) and observational studies, excluding those involving nonhuman subjects, observational studies with sample sizes under 30, interventional studies with no comparator group, commentary pieces, letters, or conference abstracts already published in full. Eligible studies involved adults (≥18 years) using medicinal cannabinoids to treat any of the conditions specified above, whether as primary treatment targets or secondary symptoms of other medical conditions. Interventions of any formulation, dose, or type of medicinal cannabinoid were included and categorised as either pharmaceutical grade THC (with or without CBD), pharmaceutical grade CBD, or herbal medicinal cannabis. We placed no restrictions on comparators, and eligible studies included those using placebo, active non-cannabinoid controls, no intervention or waitlist groups as comparators. No outcome restrictions were applied; studies meeting the inclusion criteria were retained even if they did not report outcomes directly relevant to the review and were incorporated into descriptive analyses.

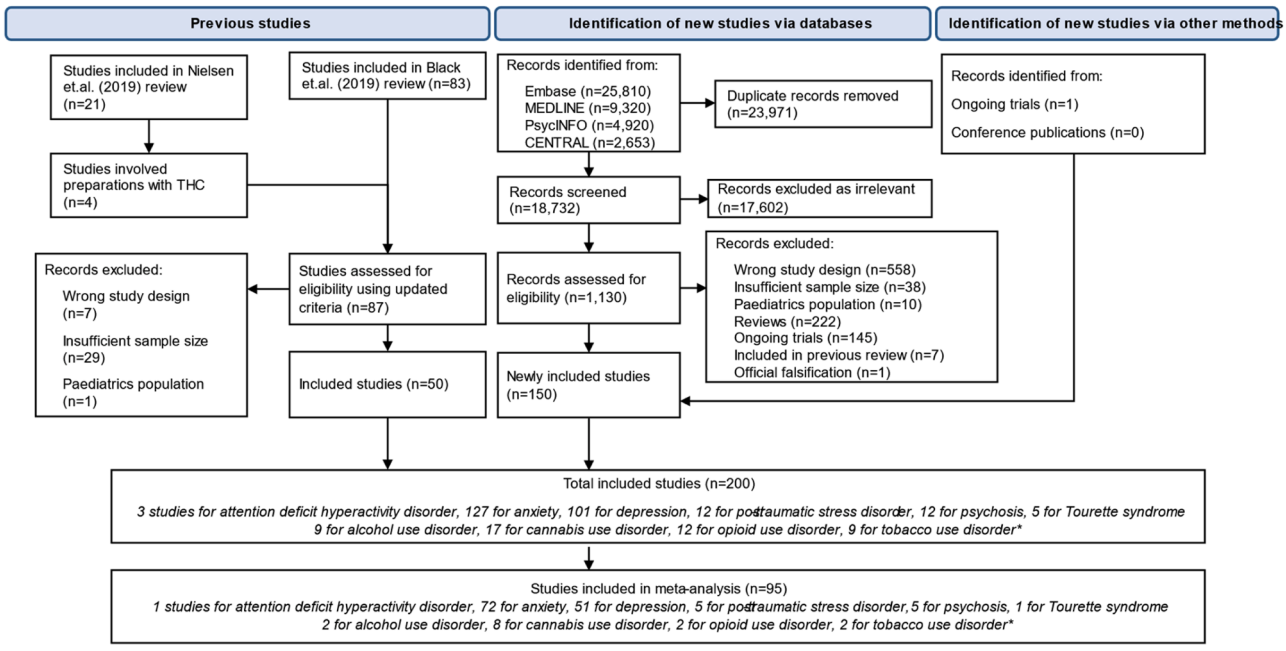
Table 1
Primary and secondary outcomes considered for each condition.

Disorder	Primary outcomes
Depression	Remission – absence of a depressive disorder diagnosis using validated scales Change in depressive symptoms using self-report scales or items
Anxiety	Remission –absence of an anxiety disorder diagnosis using validated scales Change in anxiety symptoms using self-report scales or items
PTSD	Remission –absence of a PTSD diagnosis using validated scales Change in PTSD symptoms using self-report scales or items
Psychosis	Remission – absence of a psychosis disorder diagnosis using validated scales Change in overall, positive and negative symptoms of psychosis
ADHD	Remission – absence of an ADHD diagnosis using validated scales Change in ADHD symptoms using self-report scales or items
Tourette syndrome	Remission – absence of a Tourette syndrome diagnosis using validated scales Change in tic severity measured using self-report scales or items
Substance use disorder (alcohol, cannabis, opioid, tobacco)	Remission – the absence of a substance use disorder diagnosis using validated scales Change in substance use disorder symptoms Change in withdrawal symptoms using self-report scales or items Change in craving symptoms using self-report scales or items
All disorders (controlled trials only)	Adverse events, all-cause Serious adverse events as defined by authors, all-cause Treatment-related adverse events, all-cause Study withdrawals, all-cause Study withdrawals due to adverse events

2.3. Study selection and data extraction

Study team members (CT, SG, GC, XH, OT, LD, SP, SN, ZW, TS, CB) independently examined titles and abstracts, and full texts, with at least two team members independently reviewing each article. Discrepancies were resolved by group consensus with three or more team members.

One reviewer (XH) extracted data from included studies using a predeveloped form for-purpose in REDCap electronic data capture tools, with a second reviewer (CT, SG) subsequently double-checking the extractions (Harris et al., 2019). Extracted data included: (1) article information, (2) study design, and (3) study results; a complete list of outcomes of interest by disorder is provided in Table 1. A full list of extracted variables can be found in **Appendix B**. Where multiple time points were available, data were extracted from the longest reported follow-up timepoint. Where studies reported multiple eligible outcomes, each outcome was analysed separately in its own meta-analysis. Where a study contributed multiple intervention arms, arms involving the same cannabis type were combined into a single group, with weighted average means and pooled standard deviations calculated across arms. Where arms involved different cannabis types, each arm was analysed



	Experimental studies (n=82)		Non-experimental studies (n=118)	
	Included in meta-analysis (n=45)	Not incuded in meta-analysis (n=37)	Included in meta-analysis (n=50)	Not incuded in meta-analysis (n=68)
Attention deficit hyperactivity disorder	1	1	0	1
Anxiety	32	19	40	36
Depression	20	18	31	32
Post-traumatic stress disorder	1	2	4	5
Psychosis	4	5	1	2
Tourette syndrome	0	3	1	1
Alcohol use disorder	2	0	0	7
Cannabis use disorder	8	6	0	3
Opioid use disorder	2	0	0	10
Tobacco use disorder	2	0	0	7

*Numbers not exclusive.

Fig. 1. PRISMA flow diagram.

separately within the relevant comparison. Data from intention-to-treat analyses were extracted wherever available.

2.4. Statistical analysis

Where published data permitted, we computed standardised mean difference (SMD) for continuous symptom outcomes reported in two-arm studies, and standardised mean change (SMC) for single-arm studies. We computed the odds ratios (OR) for adverse events and withdrawals reported in randomised controlled trials (RCTs). We conducted separate meta-analyses by study design (experimental and observational), comparator type (active and placebo comparators), and cannabinoid type. Crossover trials were analysed using paired data. We used random effects model for RCTs and observational studies to account for heterogeneity. We conducted sensitivity analyses excluding studies with high risk of bias. All analyses were performed in RStudio 2024.12.1 using the *meta* packages (Posit team 2025; Balduzzi et al., 2019).

We interpreted SMDs of 0.2, 0.5, and 0.8 as small, medium, and large effects, respectively. Using the I^2 statistic, we assessed the level of heterogeneity between studies, with values of 0-39%, 40-74%, and 75-100% considered unimportant, moderate/substantial, and high levels of inconsistency, respectively.

We assessed experimental studies using RoB 2.0, with studies from previous reviews reassessed (Sterne et al., 2019). For observational studies, we used ROBINS-I (2024 version) when a comparator group was included, as this tool is designed specifically for comparative studies (Sterne et al., 2016). For single-arm observational studies, we used the Newcastle-Ottawa Scale (Wells et al., 2012). Two reviewers (XH, SG, SK) independently rated each study, with conflicts resolved by a third reviewer (CT). We applied an adapted version of the GRADE framework to assess the certainty of evidence for each outcome (Prasad, 2024), based on risk of bias, indirectness, inconsistency, imprecision, and publication bias. GRADE assessment criteria are included in **Appendix C.** Publication bias and small-study effects were examined using funnel plots for each meta-analysis containing a sufficient number of studies. Industry sponsorship and commercial cannabis clinic data were not incorporated into our risk-of-bias or GRADE assessments.

3. Results

3.1. Study selection

We identified 18,732 articles from our new searches, 150 of which were new and eligible (see Figure 1 for flow-chart, **Appendix D** for articles excluded during full-text review, and **Appendix E** for ongoing trials). Combined with studies from the previous review, yielded a total of 199 studies (200 records) included in this review (Toth et al., 2012). Among eligible studies (see **Appendix F** for study characteristics), the most common primary condition studied was anxiety (k=127) (Hansen et al., 2023; Toth et al., 2012; Herrmann et al., 2019; Appiah-Kusi et al., 2020; Bergamaschi et al., 2011; Gilman et al., 2022; Hardy et al., 2023; Kolobaric et al., 2023; Pinto et al., 2024; Skrabek et al., 2008; Dujic et al., 2024; Allsop et al., 2014; de Andrade Silva et al., 2024; Gundugurti et al., 2024; Kolobaric et al., 2024; Mitarnun et al., 2025; Narayan et al., 2024; Aragona et al., 2009; Crippa et al., 2011; López-Sendón Moreno et al., 2016; Müller-Vahl et al., 2001; Pini et al., 2012; Ware et al., 2010; Weber et al., 2010; de Meneses-Gaya et al., 2021; Freeman et al., 2020; Gournay et al., 2023; Hurd et al., 2019; Mongeau-Perusse et al., 2022; Rog et al., 2005; Stanley et al., 2022;

Table 2
Summary of included experimental trials (n=82)[a,b].

	Total	ADHD	Anxiety	Depression	PTSD	Psychosis	Tourette syndrome	Alcohol use disorder	Cannabis use disorder	Opioid use disorder	Tobacco use disorder
Number of trials	82	2	51	38	3	9	3	2	14	2	2
Number of participants	8,057	127	4,324	3,944	85	484	185	172	1,673	102	174
Year of study											
1980-2010	18	-	12	13	-	2	1	-	-	-	-
2011-2020	30	1	13	11	1	4	-	1	8	2	2
2021 onwards	34	1	26	14	2	3	2	1	6	-	-
Region											
Northern Europe	13	1	8	9	-	1	-	-	2	-	-
Western Europe	10	1	6	5	-	2	3	-	-	-	-
Australia and New Zealand	7	-	4	3	-	-	-	1	5	-	1
Northern America	36	-	21	11	2	4	-	1	7	2	1
Latin America and the Caribbean	8	-	7	3	1	1	-	-	-	-	-
South-eastern Asia	1	-	1	1	-	-	-	-	-	-	-
Southern Asia	1	-	1	1	-	-	-	-	-	-	-
Southern Europe	3	-	3	3	-	-	-	-	-	-	-
Multiple regions	3	-	-	2	-	1	-	-	-	-	-
Median study size (IQR)	48 (33-97)	64 (47-80)	46 (31-79)	45 (30-133)	33 (22-38)	42 (35-52)	64 (44-81)	86 (65-107)	128 (73-130)	51 (47-56)	87 (67-108)
Participant age, years M (SD)	40.11 (10.71)	37.23 (0.95)	40.01 (11.61)	45.06 (10.33)	33.32 (10.24)	34.65 (7.15)	35.45 (2.13)	35.55 (0.77)	33.60 (3.72)	43.90 (8.34)	33.60 (1.99)
% studies where primary indication was the disorder of interest		50	20	3	100	89	100	50	86	100	0
Primary indication											
ADHD	1	1	-	-	-	-	-	-	-	-	-
Anxiety	10	-	10	1	-	-	-	-	-	-	-
Depression	1	-	1	1	-	-	-	-	-	-	-
PTSD	4	-	2	-	3	-	-	-	-	-	-
Psychosis	9	-	1	1	-	8	-	-	-	-	-
Tics	4	1	3	2	-	-	3	-	-	-	-
Alcohol use disorder	1	-	-	-	-	-	-	1	-	-	-
Cannabis use disorder	12	-	5	4	-	-	-	1	12	-	2
Opioid use disorder	3	-	2	-	-	-	-	-	-	2	-
Cocaine use disorder	1	-	1	1	-	-	-	-	-	-	-
Multiple	5	-	4	3	-	1	-	-	2	-	-
Analgesic	19	-	12	17	-	-	-	-	-	-	-
Cancer	1	-	1	1	-	-	-	-	-	-	-
Other	11	-	9	7	-	-	-	-	-	-	-
Place in therapeutic hierarchy											
Primary	61	1	11	4	1	1	-	1	10	2	1
Adjuvant	21	1	40	34	2	8	3	1	4	-	1
Studies with cannabinoid-naïve participants only	2	-	2	1	-	1	-	-	NA	-	-
Studies with cannabinoid-exposure participants only	3	-	1	3	-	1	-	-	NA	-	-
Cannabinoid-naïve participants	223	74	209	125	-	1	81	-	NA	-	-
Cannabinoid used											
Cannabis sativa (plant preparations)	10	-	4	6	-	3	-	-	-	-	-
CBD	31	-	24	10	2	4	-	1	2	1	-
THC	23	-	13	10	1	2	1	-	5	1	1
CBD+THC	16	2	7	10	-	-	2	1	6	-	1
Mixed/undefined	3	-	3	3	-	-	-	-	1	-	-
Route of administration											
Oral mucosal spray	15	2	6	9	-	-	2	1	6	-	1
Capsules/tablets/drops	56	-	40	20	3	6	1	1	6	2	1
Sublingual	1	-	1	1	-	-	-	-	-	-	-
Smoked	4	-	2	4	-	-	-	-	-	-	-
Vaporised	2	-	-	2	-	1	-	-	-	-	-
Intravenous	1	-	-	-	-	1	-	-	-	-	-
Capsules and smoked concurrently	1	-	-	-	-	1	-	-	1	-	-
Mixed	2	-	2	2	-	-	-	-	1	-	-
Timeframe of effect											
Acute (≤24 hours)	13	-	11	4	1	2	-	-	1	-	-
Prolonged (>24 hours)	69	2	40	34	2	7	3	2	13	2	2

[a] Data reported as n, median (IQR), or mean (SD). A "-" indicates zero. ADHD=attention-deficit hyperactivity disorder. PTSD=post-traumatic stress disorder. AUD=alcohol use disorder. CUD=cannabis use disorder. OUD=opioid use disorder. TUD=tobacco/nicotine use disorder. THC=Δ^9tetrahydrocannabinol. CBD=cannabidiol.

[b] Non-exclusive groups.

Abelev et al., 2022; Abrams et al., 2007; Anderson et al., 2019; Aviram et al., 2020; Bahorik et al., 2018; Bestard and Toth, 2011; Cinnamon Bidwell et al., 2024; Bolsoni et al., 2022; Bolsoni et al., 2022; Burdinski et al., 2024; Cahill et al., 2021; Ciesluk et al., 2024; Cooke et al., 2023; Cowley et al., 2025; Cuttler et al., 2018; Datta et al., 2025; Datta et al., 2025; de Vries et al., 2017; Dugosh et al., 2023; Ergisi et al., 2022; Erridge et al., 2021; Erridge et al., 2023; Fabre and McLendon, 1981; Ferretti et al., 2024; Fischer et al., 2023; Francis et al., 2024; Frank et al., 2008; Gruber et al., 2021; Gulbransen et al., 2020; Gupta et al., 2024; Halman et al., 2025; Harris et al., 2022; Hua et al., 2023; Hundal et al., 2018; Ittiphakorn et al., 2023; Kalaba et al., 2021; Kasvis et al., 2022; Kawka et al., 2021; Kerlin et al., 2018; Kudahl et al., 2021; Kuhathasan et al., 2022; Kwee et al., 2022; Kwee et al., 2024; LaFrance et al., 2020; Lee et al., 2022; Leen-Feldner et al., 2022; Macari et al., 2020; Malik et al., 2016; Mangoo et al., 2022; Martin et al., 2021; Martin-Willett et al., 2024; Mazza, 2021; Minhas and Lunn, 2023; Montebello et al., 2022; Muller-Vahl et al., 2003; Muller-Vahl et al., 2023; Murphy et al., 2024; Murphy et al., 2024; Narang et al., 2008; Nathan et al., 2023; Nayak et al., 2024; Notcutt et al., 2004; Nugent et al., 2018; Olsson et al., 2023; Pillai et al., 2022; Piumatti, 2019; Poli et al., 2018; Poli et al., 2018; Rapin et al., 2021; Rifkin-Zybutz et al., 2023; Ross et al., 2021; Sachedina et al., 2022; Sagar et al., 2021; Sarid et al., 2018; Schlienz et al., 2021; Schubert et al., 2023; Shannon et al., 2019; Sotoodeh et al., 2023; Sridharan et al., 2025; Stack et al., 2023; Stienrut et al., 2024; Stith et al., 2018; Stith et al., 2020; Stith et al., 2023; Tait et al., 2023; Tait et al., 2023; Tait et al., 2025; Tervo-Clemmens et al., 2022; Vickery et al., 2022; Vivek et al., 2024; Wall et al., 2019; Wang et al., 2021; Warner-Levy et al., 2024; Weber et al., 2009; Yang et al., 2023) followed by depression (k=101) (Hansen et al., 2023; Toth et al., 2012; Gilman et al., 2022; Hardy et al., 2023; Pinto et al., 2024; Allsop et al., 2014; de Andrade Silva et al., 2024; Gundugurti et al., 2024; Mitarnun et al., 2025; Aragona et al., 2009; López-Sendón Moreno et al., 2016; Müller-Vahl et al., 2001; Pini et al., 2012; Ware et al., 2010; Weber et al., 2010; de Meneses-Gaya et al., 2021; Freeman et al., 2020; Rog et al., 2005; Abelev et al., 2022; Abrams et al., 2007; Anderson et al., 2019; Aviram et al., 2020; Bahorik et al., 2018; Bestard and Toth, 2011; Cinnamon Bidwell et al., 2024; Burdinski et al., 2024; Ciesluk et al., 2024; Cooke et al., 2023; Cuttler et al., 2018; Ferretti et al., 2024; Fischer et al., 2023; Frank et al., 2008; Gruber et al., 2021; Gulbransen et al., 2020; Halman et al., 2025; Hua et al., 2023; Kalaba et al., 2021; Kasvis et al., 2022; Kerlin et al., 2018; Kudahl et al., 2021; Kuhathasan et al., 2022; Malik et al., 2016; Martin et al., 2021; Mazza, 2021; Montebello et al., 2022; Muller-Vahl et al., 2023; Narang et al., 2008; Notcutt et al., 2004; Nugent et al., 2018; Poli et al., 2018; Poli et al., 2018; Rapin et al., 2021; Ross et al., 2021; Sachedina et al., 2022; Sagar et al., 2021; Schlienz et al., 2021; Sotoodeh et al., 2023; Stack et al., 2023; Stienrut et al., 2024; Stith et al., 2018; Stith et al., 2020; Stith et al., 2023; Tait et al., 2023; Tait et al., 2025; Tervo-Clemmens et al., 2022; Vickery et al., 2022; Wall et al., 2019; Wang et al., 2021; Weber et al., 2009; Wade et al., 2004; Bakewell et al., 2021; Balash et al., 2017; Ball et al., 2015; Bar-Lev Schleider et al., 2022; Crowell, 2017; Dvorak et al., 2024; Ellis et al., 2009; Feingold et al., 2020; Goldberg et al., 2022; Horsted et al., 2023; Kock et al., 2021; Lamonarca et al., 2024; Lent et al., 2024; Liang et al., 2019; Lintzeris et al., 2018; Lynskey et al., 2024; Martínez-Rodríguez et al., 2008; Myers; Novotna et al., 2011; Portenoy et al., 2012; Round et al., 2020; Shah et al., 2017; Specka et al., 2024; Tumati et al., 2022; van Amerongen et al., 2018; Ware et al., 2015; Wilsey et al., 2008; Wilsey et al., 2013; Zajicek et al., 2003; Zloczower et al., 2022), cannabis use disorder (k=17) (Herrmann et al., 2019; Gilman et al., 2022; Allsop et al., 2014; Freeman et al., 2020; Cooke et al., 2023; Hua et al., 2023; Montebello et al., 2022; Wall et al., 2019; Lintzeris et al., 2019; Levin et al., 2011; Levin et al., 2016; Trigo et al., 2018; Brunette et al., 2025; Levin et al., 2021; Lintzeris et al., 2020; Mills et al., 2022; Zongo et al., 2022), psychosis (k =12) (Goldberg et al., 2022; Kock et al., 2021; Brunette et al., 2025; McGuire et al., 2018; Hallak et al., 2010; Bhattacharyya et al., 2018; Boggs et al., 2018; Leweke et al., 2012; Navarro and Perez, 2024; D'Souza et al., 2005; Lee et al., 2022; Leweke et al., 2021), PTSD (k=12) (Bolsoni et al., 2022; Cahill et al., 2021; Ciesluk et al., 2024; Ross et al., 2021; Lynskey et al., 2024; Gournay et al., 2024; Jetly et al., 2015; Meakin et al., 2020; Cameron et al., 2014; Greer et al., 2014; Fraser, 2009; Sznitman et al., 2022), opioid use disorder (k=12) (Hurd et al., 2019; Wall et al., 2019; Liang et al., 2019; Zongo et al., 2022; Lucas et al., 2019; Boehnke et al., 2016; Pritchett et al., 2022; Guarnaccia et al., 2021; Barlowe et al., 2019; Vigil et al., 2017; Benedict et al., 2022; Bisaga et al., 2015), tobacco use disorder (k=9) (Herrmann et al., 2019; Nugent et al., 2018; Lintzeris et al., 2019; Zongo et al., 2022; Lucas et al., 2019; Guarnaccia et al., 2021; Steinberg et al., 2022; Lucas et al., 2021; Voci et al., 2020), alcohol use disorder (k=9) (Nugent et al., 2018; Ross et al., 2021; Wall et al., 2019; Lintzeris et al., 2019; Lucas et al., 2019; Guarnaccia et al., 2021; Lucas et al., 2021; Mueller et al., 2025; Lucas et al., 2020), Tourette syndrome (k=5) (Muller-Vahl et al., 2003; Muller-Vahl et al., 2023; Muller-Vahl et al., 2024; Milosev et al., 2019; Barchel et al., 2024) and ADHD (k=3) (Muller-Vahl et al., 2023; Ross et al., 2021; Cooper et al., 2017). Ninety-five studies (45 experimental, 50 observational) with 66,698 participants (n=4,071 in experimental studies, n=62,627 in observational studies) reported outcome data available for meta-analysis.

3.2. Characteristics of included studies and participants

Experimental studies had a median sample size of 48 participants, and all were RCTs (Table 2). Based on the number of trials, anxiety had the largest evidence base (k =51, n=4,324), followed by depression (k =38, n=3,944), and CUD (k =14, n=1,673). RCTs were most often conducted in North America (k =36, 44%) and studied CBD-only preparations (k =31, 38%). Oral administration dominated, with fewer studies using vaporisation, smoking, or other routes. Most trials did not consider cannabinoid exposure history.

Observational studies had a median sample size of 194 participants (Table 3). Most did not provide information about the type of cannabinoid under investigation, the route of administration or history of cannabis use. Importantly, the majority of studies contributing to the depression outcome examined depressive symptoms as secondary outcomes in populations with other primary conditions (e.g., pain, cancer, multiple sclerosis), rather than in populations with a primary diagnosis of a depressive disorder; this was also the case for anxiety outcomes.

3.3. Risk of bias of included studies

Risk of bias for studies in the meta-analyses are summarised in **Appendix G**. Overall, the majority of cross-over RCTs (80%) were rated as having some concerns, and parallel RCTs (69%) either as being at high risk or with concerns. Among two-arm observational studies, most (89%) were at serious risk of bias due to confounding and/or selection of participants. For single-arm observational studies, most (73%) were at risk of bias due to comparability, and all were at risk of bias due to participant selection.

Table 3
Summary of included observational studies (n=118)[a,b].

	Total	ADHD	Anxiety	Depression	PTSD	Psychosis	Tourette syndrome	Alcohol use disorder	Cannabis use disorder	Opioid use disorder	Tobacco use disorder
Number of trials	118	1	76	63	9	3	2	7	3	10	7
Number of participants	265,323	99	71,525	138,145	1,000	54,221	155	4,380	19,260	82,396	51,617
Year of study											
1980-1990	-	-	-	-	-	-	-	-	-	-	-
1991-1999	-	-	-	-	-	-	-	-	-	-	-
2001-2010	3	-	1	2	1	-	-	-	-	-	-
2011-2020	38	-	19	23	3	-	1	4	1	6	3
2021 onwards	77	1	56	38	5	3	1	3	2	4	4
Region											
Northern Europe	26	-	24	4	2	-	-	-	-	-	-
Western Europe	4	-	2	3	-	-	1	-	-	-	-
Australia and New Zealand	10	-	9	8	-	-	-	-	-	-	-
Northern America	63	1	35	36	7	1	-	7	3	10	7
South-eastern Asia	1	-	1	1	-	-	-	-	-	-	-
Southern Europe	4	-	3	4	-	-	-	-	-	-	-
Western Asia	8	-	2	6	-	1	1	-	-	-	-
Latin America and the Caribbean	2	-	-	1	-	1	-	-	-	-	-
Study design											
Prospective Cohort	61	1	48	32	4	1	-	1	1	1	1
Retrospective Cohort	29	-	13	15	3	2	2	-	1	3	1
Quasi-experimental design	1	-	1	-	-	-	-	-	-	-	-
Cross Sectional	25	-	12	14	2	-	-	6	1	6	5
One Arm Trial	1	-	1	1	-	-	-	-	-	-	-
Open label	1	-	1	1	-	-	-	-	-	-	-
Study size median (IQR)	194 (97-692)	99 (NA)	206 (108-550)	249 (98-891)	81 (77-104)	152 (108-27,079)	78 (67-88)	444 (107-812)	444 (304-9,549)	344 (115-2,145)	697 (383-10,343)
Participant age, years M (SD)	48.22 (10.64)	53 (NA)	47.37 (9.62)	50.89 (10.24)	41.84 (7.92)	66.59 (11.80)	33.4 (3.39)	49.2 (7.66)	43.3 (8.49)	47.57 (7.95)	48.06 (7.37)
% studies where primary indication was the disorder of interest		0	12	3	67	0	100	0	0	0	0
Primary indication											
ADHD	1	-	1	-	-	-	-	-	-	-	-
Anxiolytic	9	-	9	2	-	-	-	-	-	-	-
Depression	3	-	2	2	-	-	-	-	-	-	-
PTSD	9	-	3	1	6	-	-	-	-	-	-
Tics	2	-	-	-	-	-	2	-	-	-	-
Multiple	44	-	28	29	2	1	-	4	3	5	5
Other											
Alzheimer's	1	-	-	-	-	1	-	-	-	-	-
Analgesic	32	1	21	20	1	-	-	2	-	4	1
Cancer	6	-	6	3	-	-	-	-	-	-	-
Epilepsy	2	-	1	1	-	-	-	-	-	-	-
IBD	2	-	2	1	-	-	-	-	-	-	-
Multiple Sclerosis	2	-	1	-	-	-	-	1	-	1	1
Parkinson's disease	3	-	-	3	-	1	-	-	-	-	-
Sleep	2	-	2	1	-	-	-	-	-	-	-
Place in therapeutic hierarchy											
Primary	5	-	2	-	3	-	-	-	-	-	-
Adjuvant	114	1	74	63	6	3	2	7	3	10	7
Studies with cannabinoid-naïve participants only	1	-	1	1	-	-	-	-	NA	-	-
Studies with cannabinoid-exposure participants only	1	-	-	-	1	-	-	-	NA	-	-
Cannabinoid-naïve participants	27,317	-	23,334	20,430	-	-	-	-	NA	-	-
Cannabinoid used											
Cannabis sativa (plant preparations)	3	-	2	3	-	-	-	-	-	-	-
CBD	6	-	3	4	-	1	-	-	-	-	-
CBD+THC	3	-	3	2	-	-	-	-	-	-	-
THC	10	-	6	6	3	-	1	-	-	-	-
Mixed/undefined	100	1	64	50	6	2	2	7	3	10	7
Route of administration											

(*continued on next page*)

Table 3 (*continued*)

	Total	ADHD	Anxiety	Depression	PTSD	Psychosis	Tourette syndrome	Alcohol use disorder	Cannabis use disorder	Opioid use disorder	Tobacco use disorder
Capsules/tablets/drops	19	-	11	12	3	1	1	-	-	-	-
Oral olive oil infusion	1	-	1	1	-	-	-	-	-	-	-
Smoked	1	-	-	1	-	-	-	-	-	-	-
Mixed	98	1	64	49	6	2	2	7	3	10	7
Timeframe of effect											
Acute (≤24 hours)	-	-	-	-	-	-	-	-	-	-	-
Prolonged (>24 hours)	118	1	76	63	9	3	2	7	3	10	7

[a] Data reported as n, median (IQR), or mean (SD). A "-" indicates zero. ADHD=attention-deficit hyperactivity disorder. PTSD=post-traumatic stress disorder. AUD=alcohol use disorder. CUD=cannabis use disorder. OUD=opioid use disorder. TUD=tobacco/nicotine use disorder. THC=Δ^9tetrahydrocannabinol. CBD=cannabidiol.

[b] Non-exclusive groups.

3.4. Evidence of effects of medicinal cannabinoids on mental disorders

Table 4 summarises the pooled effects from experimental studies for mental disorders (see **Appendix H** for forest plots stratified by cannabinoid type, comparator, and study design; see **Appendix I** for a summary of observational study results). Among experimental studies, we found that medicinal cannabinoids result in a reduction of symptoms in anxiety and PTSD, but the certainty of evidence ranged from very low to moderate (Table 4). Medicinal cannabinoids had trivial to no effect on symptoms of ADHD or depression, or on total and negative symptoms of psychosis, and the certainty of evidence for these outcomes was very low; small reductions were observed in positive symptoms of psychosis and in symptoms of Tourette syndrome, also at very low certainty (Table 4).

3.4.1. ADHD

Two RCTs (n=127) evaluated the effects of cannabinoids compared to placebo on ADHD symptoms and found no evidence of an effect (SMD=-0.62; 95% CI: -1.32, 0.08). No observational studies examining cannabinoids for the treatment of ADHD were identified.

3.4.2. Anxiety

Across 41 RCT's, including 4,878 participants, there was very low certainty evidence that cannabinoids were associated with a reduction in anxiety symptoms (SMD = -0.40, 95% CI: -0.57, -0.23, I^2 = 90%).

Observational studies showed varying evidence depending on the type of study design i.e., statistically significant reductions for single-arm studies only (MC=-2.22; 95%CI: -2.88,-1.56; I^2=99%).

3.4.3. Depression

There was very low certainty evidence from RCTs that cannabinoids have no effect on reducing symptoms of depression (SMD=-0.20, 95% CI: -0.43 to 0.04, I^2=91.6%). Again, observational studies showed varying evidence depending on the type of study design i.e., a positive effect on depression was observed among single-arm studies only (MC=-2.61; 95%CI: -3.72,-1.50; I^2 = 100%).

3.4.4. Psychosis

There was very low certainty evidence from experimental studies that cannabinoids have no effect on total or negative psychosis-related symptoms. Cannabinoids were found to be associated with an improvement in positive psychosis symptoms (SMD=-0.22, 95% CI: -0.42, -0.01; I^2=4.3%). One single-arm observational study showed a reduction of total psychosis symptoms over time (MC=9.9; 95%CI: 4.09,15.71).

3.4.5. PTSD

There was moderate certainty based on a single RCT of an improvement in PTSD symptom severity associated with cannabinoid use (SMD=-2.60; 95%CI: -4.58, -0.62). It should be noted that this estimate derives from a single small RCT (n=20), yielding a wide confidence interval; while the interval excludes the null, the precision of this estimate is limited. There was evidence from both two-arm and single-arm observational studies that PTSD symptoms reduced among people using cannabinoids (MC=-4.42; 95%CI: -5.00, -3.85).

3.4.6. Tourette syndrome

There was very low certainty evidence from 3 RCT's (138 participants) that cannabinoids were associated with a reduction in Tourette syndrome compared to placebo (SMD: -0.58, 95%CI: -1.16, -0.00 I^2=37.3%). A single-arm observational study showed that symptoms of Tourette syndrome worsened over time in individuals using cannabinoids (MC=4.03; 95%CI: 0.89,7.18).

3.5. Evidence of effects of medicinal cannabinoids on substance use disorders

Table 5 summarises the pooled effects from experimental studies for substance use disorders (see **Appendix H** for forest plots stratified by cannabinoid type, comparator, and study design). No observational studies for substance use disorders reported outcome data eligible for meta-analysis. All experimental studies compared medicinal cannabinoids with placebos. Among experimental studies, we found no evidence of an effect of medicinal cannabinoids on overall or craving symptoms of alcohol use disorder, from very low certainty of evidence (Table 5). We found that medicinal cannabinoids resulted in an increase in overall symptoms of cannabis use disorder, from very low certainty of evidence, with no evidence of an effect on cannabis use disorder withdrawal or craving symptoms (Table 5). Medicinal cannabinoids resulted in a trivial to no effect on symptoms of opioid use disorder and tobacco/nicotine use disorder, and the certainty of evidence was very low (Table 5).

3.5.1. Alcohol use disorder (AUD)

Very low certainty evidence from RCTs found no difference between cannabinoids and placebo on overall and craving-related symptoms of alcohol use disorder symptoms. No RCTs examined withdrawal outcomes for AUD and no eligible observational studies were identified.

3.5.2. Cannabis use disorder (CUD)

There was very low certainty of evidence based on one RCT of a worsening of overall CUD symptom severity (i.e., greater symptom severity in the cannabinoid arm relative to placebo) associated with cannabinoid use compared with placebo (SMD=2.35; 95% CI: 1.49, 3.21). There was very low certainty evidence that cannabinoids were not associated with reduced CUD withdrawal (SMD=-0.20; 95% CI: -0.47, 0.06) or craving (SMD=-0.19; 95% CI: -0.45, 0.08) symptoms compared to placebo. No eligible observational studies were identified.

3.5.3. Opioid use disorders (OUD)

There was very low certainty of evidence based on one RCT that

Table 4
Summary of evidence from experimental studies on the use of cannabinoids for the treatment of mental disorders.

	Comparator	K Studies	N participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	SMD (95% CI)	I^2 (Kosiba et al., 2019)	Favours	GRADE
Attention-deficit hyperactivity disorder												
Change in symptom severity	Placebo	2	127	Not serious	Not serious	Not serious	Extremely serious	Likely	-0.62 (-1.32, 0.08)	0	Neither	Very low
Anxiety												
Change in symptom severity	Placebo	34	3562	Serious	Serious	Serious	Not serious	Likely	-0.40 (-0.57, -0.23)	90.0	Cannabinoids	Very low
	Active	7	1316									
Depression												
Change in symptom severity	Placebo	23	2370	Serious	Serious	Serious	Very serious	Likely	-0.20 (-0.43, 0.04)	91.6	Neither	Very low
	Active	2	83									
Psychosis												
Change in total symptoms	Placebo	3	208	Serious	Not serious	Not serious	Very serious	Likely	-0.01 (-0.25, 0.22)	0.9	Neither	Very low
	Active	2	70									
Change in positive symptoms	Placebo	4	232	Serious	Not serious	Not serious	Serious	Undetected	-0.22 (-0.42, -0.01)	4.3	Cannabinoids	Very low
	Active	1	39									
Change in negative symptoms	Placebo	4	232	Serious	Not serious	Not serious	Serious	Likely	0.11 (-0.19, 0.41)	36.6	Neither	Very low
	Active	1	39									
Post-traumatic stress disorder												
Change in symptom severity	Placebo	1	20	Not serious	Not serious	Serious	Not serious	Undetected	-2.60 (-4.58, -0.62)	NA	Cannabinoids	Moderate
	Active	0	-									
Tourette syndrome												
Change in symptom severity	Placebo	3	138	Not serious	Not serious	Not serious	Extremely serious	Undetected	-0.58 (-1.16, 0.00)	37.3	Cannabinoids	Very low
	Active	0	0									

SMD=standardised mean difference. GRADE=Grading of Recommendations, Assessment, Development and Evaluation. NA=not applicable. THC=Δ^9tetrahydrocannabinol. CBD=cannabidiol. Outcomes for which forest plots available are in the appendix H. In all comparisons the control group (placebo or active) is the reference group.

cannabinoids had no effect on OUD-related withdrawal symptoms compared with placebo (SMD=3.28; 95%CI: -5.53, 12.09). There was also very low certainty of evidence of no effect of cannabinoids compared with placebo on OUD craving-related symptoms (SMD=-0.21; 95%CI: -0.74, 0.31). None of the included RCTs reported on overall OUD symptoms and no eligible observational studies were identified.

3.5.4. *Tobacco use disorder (TUD)*

There was very low certainty of evidence based on one RCT of no difference between cannabinoids and placebo on overall TUD symptoms. Similarly, there was very low certainty evidence of no difference between cannabinoids and placebo on TUD craving symptoms. No RCTs examined withdrawal symptoms in TUD and no eligible observational studies were identified.

3.6. *Evidence of effects of medicinal cannabinoids on safety from RCTs*

Overall, the evidence quality is very low across most outcomes and cannabinoid types.

Pooled odds ratios suggested variable safety profiles. The only statistically significant safety finding was for THC, which was associated with increased withdrawals due to adverse events compared with placebo (OR=2.78; 95%CI: 1.66, 4.65; 15 trials, n=1,758; I^2=0%). CBD showed an imprecise signal towards increased all-cause adverse events compared to placebo (OR=2.63; 95%CI: 0.67, 10.34; I^2=66.7%), while CBD-THC combinations showed pooled ORs of 1.57 (95% CI: 0.68, 3.60) for serious adverse events and 1.80 (95% CI: 0.34, 9.61) for withdrawals due to adverse events; the confidence intervals for each of these estimates include the null. Substantial heterogeneity was noted in several analyses (e.g., I^2=58.4-76.4%), and most outcomes were downgraded due to serious or extremely serious concerns regarding indirectness, inconsistency, and imprecision (Table 6).

4. Discussion

This systematic review and meta-analysis provide an up-to-date synthesis of evidence from studies examining the effects of medicinal cannabinoids across a range of mental and substance use disorders and symptoms. Among experimental studies, there was very low to moderate certainty of evidence of benefit for anxiety and PTSD, no evidence of benefit for depression, and very low to low certainty of evidence of trivial to no effect on ADHD, psychosis and Tourette syndrome. For substance use disorders, cannabinoids worsened overall cannabis use disorder symptom severity in a single trial, with no clear effect on cannabis craving or withdrawal, or on AUD, OUD or TUD. Safety evidence was predominantly very low certainty; THC was associated with increased withdrawals due to adverse events compared with placebo (OR=2.78; 95%CI: 1.66, 4.65), the only statistically significant safety finding in the review, while signals for CBD (all-cause adverse events) and CBD-THC combinations (serious adverse events and withdrawals) were imprecise; these safety signals are clinically important and should weigh heavily in any consideration of cannabinoid use for these populations. Among observational studies, there appears to be some evidence for improvements in anxiety, depression, psychosis and PTSD symptoms; however, these studies were considered to be at high risk of bias. Notably, evidence for depression, and to a lesser extent anxiety, largely comes from studies where these conditions were not the primary indication: depression was the primary indication in only 3% of contributing trials, and anxiety in 20% (Table 2). That is, many findings reflect changes in depressive or anxiety symptoms measured as secondary outcomes in populations with pain, cancer, multiple sclerosis, or other primary medical conditions, rather than the treatment of established psychiatric disorders. The pooled estimates for these outcomes should therefore not be equated with evidence of efficacy for primary anxiety or depressive disorders. Furthermore, the three cannabinoid categories examined (pharmaceutical-grade THC, pharmaceutical-grade

Table 5
Summary of evidence from experimental studies on the use of cannabinoids for the treatment of substance use disorders.

	Comparator	K studies	N participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	SMD (95% CI)	*I* (Kosiba et al., 2019)	Favours	GRADE
Alcohol use disorder												
Change in overall symptom severity	Placebo	1	128	Very serious	Very serious	Serious	Extremely serious	Undetected	-1.30 (-3.03, 0.43)	NA	Neither	Very low
Change in withdrawal symptom severity	-	0	-	-	-	-	-	-	-	-	-	-
Change in craving symptom severity	Placebo	1	44	Very serious	Not serious	Serious	Extremely serious	Undetected	0.30 (-0.52, 1.12)	NA	Neither	Very low
Cannabis use disorder												
Change in overall symptom severity	Placebo	1	186	Very serious	Serious	Serious	Very serious	Undetected	2.35 (1.49, 3.21)	NA	Comparators	Very low
Change in withdrawal symptom severity	Placebo	3	221	Serious	Not serious	Not serious	Very serious	Undetected	-0.20 (-0.47, 0.06)	0	Neither	Very low
Change in craving symptom severity	Placebo	2	220	Very serious	Serious	Not serious	Very serious	Undetected	-0.19 (-0.45, 0.08)	0	Neither	Very low
Opioid use disorder												
Change in overall symptom severity	-	0	-	-	-	-	-	-	-	-	-	-
Change in withdrawal symptom severity	Placebo	1	60	Very serious	Not serious	Serious	Extremely serious	Undetected	3.28 (-5.53, 12.09)	NA	Neither	Very low
Change in craving symptom severity	Placebo	2	57	Not serious	Not serious	Not serious	Extremely serious	Undetected	-0.21 (-0.74, 0.31)	0	Neither	Very low
Tobacco/nicotine use disorder												
Change in overall symptom severity	Placebo	1	128	Very serious	Very serious	Serious	Extremely serious	Undetected	0.30 (-0.63, 1.23)	NA	Neither	Very low
Change in withdrawal symptom severity	-	0	-	-	-	-	-	-	-	-	-	-
Change in craving symptom severity	Placebo	1	92	Very serious	Very serious	Serious	Extremely serious	Undetected	-2.18 (-6.59, 2.23)	NA	Neither	Very low

SMD=standardised mean difference. GRADE=Grading of Recommendations, Assessment, Development and Evaluation. NA=not applicable. THC=Δ^9tetrahydrocannabinol. CBD=cannabidiol. In all comparisons the control group (placebo or active) is the reference group.

Table 6
Summary of evidence from experimental studies on the safety of cannabinoids use for medicinal purposes.

	Comparator	K studies	N participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled OR (95% CI)	I^2	Groups with more adverse events or withdrawals	GRADE
CBD												
Adverse events, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	3	161	Serious	Serious	Serious	Extremely serious	Likely	2.63 (0.67, 10.34)	66.7	Cannabinoids	Very low
Adverse events, serious	Active	1	39	Not serious	Not serious	Serious	Extremely serious	Undetected	5.27 (0.24, 117.25)	NA	Cannabinoids	Very low
	Placebo	3	231	Very serious	Very serious	Not serious	Extremely serious	Undetected	1.50 (0.44, 5.19)	0	Cannabinoids	Very low
Withdrawals, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	2	116	Not serious	Serious	Not serious	Extremely serious	Likely	1.31 (0.33, 5.18)	0	Cannabinoids	Very low
Withdrawals, due to adverse events	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	3	136	Very serious	Not serious	Not serious	Extremely serious	Undetected	1.35 (0.28, 6.46)	0	Cannabinoids	Very low
THC												
Adverse events, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	1	60	Very serious	Not serious	Serious	Extremely serious	Undetected	1.68 (0.04, 6.86)	NA	Cannabinoids	Very low
Adverse events, serious	Active	2	182	Not serious	Not serious	Not serious	Extremely serious	Undetected	1.44 (0.54, 3.81)	0	Cannabinoids	Very low
	Placebo		216	Not serious	Not serious	Serious	Extremely serious	Undetected	0.84 (0.11, 6.70)	NA	Comparator	Very low
Adverse events, treatment-emergent	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	1	19	Very serious	Not serious	Serious	Extremely serious	Undetected	0.54 (0.09, 3.12)	NA	Comparator	Very low
Withdrawals, all-cause	Active	2	182	Not serious	Very serious	Serious	Extremely serious	Undetected	0.55 (0.04, 5.85)	66.4	Comparator	Very low
	Placebo	4	261	Very serious	Serious	Not serious	Extremely serious	Undetected	0.64 (0.37, 1.09)	0	Comparator	Very low
Withdrawals, due to adverse events	Active	2	252	Not serious	Very serious	Not serious	Extremely serious	Undetected	0.54 (0.17, 1.68)	0	Comparator	Very low
	Placebo	15	1,758	Serious	Serious	Not serious	Extremely serious	Likely	2.78 (1.66, 4.65)	0	Cannabinoids	Very low
CBD-THC												
Adverse events, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	2	225	Serious	Serious	Very serious	Extremely serious	Likely	1.99 (0.40, 9.85)	76.4	Cannabinoids	Very low
Adverse events, treatment-emergent	Active	-	-	-	-	-	-	-		-	-	-
	Placebo	2	53	Serious	Serious	Not serious	Extremely serious	Undetected	0.69 (0.10, 4.73)	0	Comparator	Very low
Adverse events, serious	Active			-	-	-	-	-		-	-	-
	Placebo	7	435	Serious	Serious	Not serious	Extremely serious	Undetected	1.57 (0.68, 3.60)	0	Cannabinoids	Very low
Withdrawals, all-cause	Active			-	-	-	-	-		-	-	-
	Placebo	5	476	Very serious	Serious	Serious	Extremely Serious	Undetected	1.08 (0.50, 2.30)	58.4	Cannabinoids	Very low
Withdrawals, due to adverse events	Active			-	-	-	-	-		-	-	-
	Placebo	2	225	Serious	Serious	Not serious	Extremely serious	Likely	1.80 (0.34, 9.61)	11.4	Cannabinoids	Very low

(*continued on next page*)

Table 6 (*continued*)

	Comparator	K studies	N participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled OR (95% CI)	I^2	Groups with more adverse events or withdrawals	GRADE
Mixed												
Adverse events, treatment-emergent	Placebo	1	216	Very serious	Serious	Serious	Extremely serious	Undetected	1.79 (1.00, 3.20)	NA	Cannabinoids	Very low
Adverse events, serious	Placebo	1	69	Serious	Serious	Serious	Extremely serious	Undetected	1.24 (0.20, 7.63)	NA	Cannabinoids	Very low
Plant												
Adverse events, serious	Placebo	1	31	Very serious	Serious	Serious	Extremely serious	Undetected	3.00 (0.11, 79.50)	NA	Cannabinoids	Very low
	Comparator	**K studies**	**N participants**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Pooled OR (95% CI)**	**I^2**	**Groups with more adverse events or withdrawals**	**GRADE**
CBD												
Adverse events, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	3	161	Serious	Serious	Serious	Extremely serious	Likely	2.63 (0.67, 10.34)	66.7	Cannabinoids	Very low
Adverse events, serious	Active	1	39	Not serious	Not serious	Serious	Extremely serious	Undetected	5.27 (0.24, 117.25)	NA	Cannabinoids	Very low
	Placebo	3	231	Very serious	Very serious	Not serious	Extremely serious	Undetected	1.50 (0.44, 5.19)	0	Cannabinoids	Very low
Withdrawals, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	2	116	Not serious	Serious	Not serious	Extremely serious	Likely	1.31 (0.33, 5.18)	0	Cannabinoids	Very low
Withdrawals, due to adverse events	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	3	136	Very serious	Not serious	Not serious	Extremely serious	Undetected	1.35 (0.28, 6.46)	0	Cannabinoids	Very low
THC												
Adverse events, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	1	60	Very serious	Not serious	Serious	Extremely serious	Undetected	1.68 (0.04, 6.86)	NA	Cannabinoids	Very low
Adverse events, serious	Active	2	182	Not serious	Not serious	Not serious	Extremely serious	Undetected	1.44 (0.54, 3.81)	0	Cannabinoids	Very low
	Placebo	2	216	Not serious	Not serious	Serious	Extremely serious	Undetected	0.84 (0.11, 6.70)	NA	Comparator	Very low
Adverse events, treatment-emergent	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	1	19	Very serious	Not serious	Serious	Extremely serious	Undetected	0.54 (0.09, 3.12)	NA	Comparator	Very low
Withdrawals, all-cause	Active	2	182	Not serious	Very serious	Serious	Extremely serious	Undetected	0.55 (0.04, 5.85)	66.4	Comparator	Very low
	Placebo	4	261	Very serious	Serious	Not serious	Extremely serious	Undetected	0.64 (0.37, 1.09)	0	Comparator	Very low
Withdrawals, due to adverse events	Active	2	252	Not serious	Very serious	Not serious	Extremely serious	Undetected	0.54 (0.17, 1.68)	0	Comparator	Very low
	Placebo	15	1,758	Serious	Serious	Not serious	Extremely serious	Likely	2.78 (1.66, 4.65)	0	Cannabinoids	Very low
CBD-THC												
Adverse events, all-cause	Active	0	-	-	-	-	-	-	-	-	-	-
	Placebo	2	225	Serious	Serious	Very serious	Extremely serious	Likely	1.99 (0.40, 9.85)	76.4	Cannabinoids	Very low
Adverse events, treatment-emergent	Active	-	-	-	-	-	-	-		-	-	-
	Placebo	2	53	Serious	Serious	Not serious	Extremely serious	Undetected	0.69 (0.10, 4.73)	0	Comparator	Very low
Adverse events, serious	Active			-	-	-	-	-		-	-	-

(*continued on next page*)

Table 6 (*continued*)

	Comparator	K studies	N participants	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled OR (95% CI)	I^2	Groups with more adverse events or withdrawals	GRADE
	Placebo	7	435	Serious	Serious	Not serious	Extremely serious	Undetected	1.57 (0.68, 3.60)	0	Cannabinoids	Very low
Withdrawals, all-cause	Active			-	-	-	-	-		-	-	-
	Placebo	5	476	Very serious	Serious	Serious	Extremely Serious	Undetected	1.08 (0.50, 2.30)	58.4	Cannabinoids	Very low
Withdrawals, due to adverse events	Active			-	-	-	-	-		-	-	-
	Placebo	2	225	Serious	Serious	Not serious	Extremely serious	Likely	1.80 (0.34, 9.61)	11.4	Cannabinoids	Very low
Mixed												
Adverse events, treatment-emergent	Placebo	1	216	Very serious	Serious	Serious	Extremely serious	Undetected	1.79 (1.00, 3.20)	NA	Cannabinoids	Very low
Adverse events, serious	Placebo	1	69	Serious	Serious	Serious	Extremely serious	Undetected	1.24 (0.20, 7.63)	NA	Cannabinoids	Very low
Plant												
Adverse events, serious	Placebo	1	31	Very serious	Serious	Serious	Extremely serious	Undetected	3.00 (0.11, 79.50)	NA	Cannabinoids	Very low

*Sensitivity analysis excluding high risk of bias studies indicated no difference in pooled effects.

CBD, and herbal medicinal cannabis) differ substantially in pharmacology, dosing reliability, psychiatric risk profile, and regulatory status; clinically important distinctions between these categories should be borne in mind when interpreting pooled analyses.

4.1. Implications

Research in this area has expanded, with 150 new studies identified. However, the overall quality of the evidence remains low, due to limitations in study designs, sample size, risk of bias and the duration of studies, reflecting the lack of robust high-quality trials. Additionally, our examination of the evidence identified few studies relevant to alcohol, opioid and tobacco use disorders, and all related evidence was rated as low quality.

Another limitation was the lack of harmonisation across the research landscape, with heterogeneity relating to participant samples but also outcome selection, measurement tools, formulations, dosing regimens, and routes of administration. This is particularly relevant given that most people accessing cannabis for mental or substance use disorders are likely to be obtaining plant-based products with greater THC potency and lower CBD concentrations, whereas the experimental evidence has predominantly focused on pharmaceutical preparations with lower THC doses (Lowe et al., 2019). Accordingly, any therapeutic potential of medicinal cannabinoids must be interpreted alongside evidence that nonmedical or high-THC cannabis exposure is associated with worse depressive and manic symptoms and an elevated risk of adverse mood disorder outcomes (Sorkhou et al., 2024).

Although some promising findings warrant further investigation, particularly for anxiety, the existing evidence remains insufficient to support medicinal cannabinoids as a first-line treatment for mental and substance use disorders, especially given the availability of alternative interventions with a substantially stronger evidence base and more favourable certainty ratings (Lowe et al., 2019; Leichsenring et al., 2022; Dellazizzo et al., 2023; Volkow and Blanco, 2023). This is consistent with a recent review concluding that evidence is insufficient for the use of cannabis or cannabinoids for most medical indications, and emphasising that clinicians should weigh the benefits against risk when engaging patients in informed discussions about use (Hsu et al., 2026). Through our searches, we identified 33 ongoing or incomplete trials, with 17 trials still ongoing, which may potentially provide higher-quality evidence. However, until high-quality evidence is available, caution should be exercised when considering medicinal cannabinoids for these conditions.

4.2. Strengths and limitations

This study included a comprehensive search with no language limit and inclusion of both experimental and observational studies. It extended and expanded on previous reviews, providing evidence stratified by cannabinoid and comparator type, differentiating the differences between placebo and active comparators. Even so, where meta-analyses were conducted, the clinical and methodological heterogeneity across included studies meant that pooled estimates should be interpreted with caution, as they may obscure important variation in effects across subgroups. Further, where the diversity of study designs and outcome measures precluded meta-analysis, particularly amongst observational studies, no formal synthesis was undertaken. Data extraction was performed by one reviewer and verified by a second, which, while reducing the likelihood of error, does not constitute fully independent duplicate extraction and may represent a potential source of bias. The imprecision criteria applied during GRADE rating, whereby only confidence intervals crossing the null effect triggered downgrading, represents a specific methodological choice that may yield higher certainty ratings than alternative approaches, particularly for outcomes derived from small single studies with wide confidence intervals, and readers should interpret such ratings accordingly. Additionally,

although the serious risk of bias and high heterogeneity among observational studies means that their findings should not be interpreted as evidence of effectiveness, some descriptions of observational results in this review reflect improvements observed over time rather than controlled treatment effects, and readers should interpret such findings with this important caveat in mind.

5. Conclusion

Across a broad range of mental and substance use disorders, the current evidence base for medicinal cannabinoids is characterised by predominantly very low certainty, high heterogeneity and substantial methodological limitations, precluding firm conclusions about efficacy and safety. While some promising signals exist, particularly for anxiety, these findings should be interpreted cautiously and are insufficient to support medicinal cannabinoids as a first-line treatment where alternatives with stronger evidence bases exist. Continued investment in high-quality research is needed to clarify the therapeutic potential of cannabinoids and inform evidence-based clinical guidance in this rapidly evolving field.

Author contributions

This review was conceived by LD and MF along with GC, CT, SG, SN, and CB. CB closely oversaw and supervised the analysis. XH undertook the analyses. CB led the write-up of the manuscript along with GC and LD. All authors were involved in decisions about the scope of the manuscript, decisions about study eligibility, and critically reviewing the analysis of the data. All authors were involved in critically reviewing the manuscript.

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Declaration of competing interest

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Supplementary materials

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