The efficacy and safety of cannabinoids for the treatment of mental disorders and substance use disorders: a systematic review and meta-analysis

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Summary

Background Mental disorders and substance use disorders (SUDs) are among the leading reasons for which the medical use of cannabinoids has been approved, but their efficacy and safety in treating these conditions is yet to be established. We conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) testing the efficacy and safety of cannabinoids as the primary treatment for mental disorders or SUDs.

Methods We searched Ovid MEDLINE, PsychINFO, Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, and Embase for peer-reviewed articles published between Jan 1, 1980, and May 13, 2025, evaluating the efficacy of cannabinoids in reducing or treating mental disorders and SUDs as the primary indication. Primary outcomes were remission of disorder or reduction in disorder symptoms. Safety was assessed via synthesis of all-cause and serious adverse events, which was used to calculate the number needed to treat to harm (NNTH). Two independent reviewers screened all studies and performed data extraction. Evidence was synthesised as odds ratios (ORs) for dichotomous measures and standardised mean differences (SMDs) for continuous measures, via random-effects meta-analysis in Review Manager, version 5.4. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias 2.0 tool. We evaluated the quality of the primary outcomes using the GRADE framework. The study was registered with PROSPERO (CRD42023392718).

Findings 54 trials were identified for inclusion (2477 participants; 1713 [69%] males, 764 [31%] females; median age 33·3 years [IQR 28·1–38·05; ethnicity data not available). 24 (44%) of these trials had a high risk of bias, and the certainty of evidence for most outcomes was low. Our meta-analysis revealed that a combination of cannabidiol and delta-9-tetrahydrocannabinol reduced cannabis withdrawal symptoms (SMD –0·29, 95% CI –0·57 to –0·02) and weekly grams of cannabis use (–1·00, –1·69 to –0·30) among those with cannabis use disorder, and a reduction in tic severity among those with tic or Tourette's Syndrome (–0·68, –1·03 to –0·34) compared with placebo. Any cannabinoid type led to an increase in sleep time as recorded by an electronic device (0·54, 0·14 to 0·95) and sleep diary (0·55, 0·01 to 1·09) among those with insomnia. There was a reduction in autistic traits (–0·36, –0·66 to –0·07) among those with autism spectrum disorder. Cannabinoids led to an increase in cocaine craving among those with cocaine use disorder (0·69, 0·22 to 1·15) compared with placebo. There were no significant effects on outcomes associated with anxiety, anorexia nervosa, psychotic disorders, post-traumatic stress disorder, and opioid use disorder. There were insufficient data to meta-analyse studies of ADHD, bipolar disorder, obsessive-compulsive disorder, and tobacco use disorder. There was an absence of RCT evidence for the treatment of depression. Meta-analysis revealed higher odds of all-cause adverse events (OR 1·75, 95% CI 1·25 to 2·46) among those using cannabis versus control group (NNTH=7) but no higher odds of serious adverse events or study withdrawal.

Interpretation There was some evidence that cannabinoids can reduce symptoms of cannabis use disorder, insomnia, tic or Tourette's syndrome, and autism spectrum disorder, but the quality of this evidence was generally low. Cannabinoids were associated with a greater risk of any adverse events but not of serious adverse events. Overall, there is a crucial need for more high-quality research. Given the scarcity of evidence, the routine use of cannabinoids for the treatment of mental disorders and SUDs is currently rarely justified.

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Introduction

Mental disorders and substance use disorders (SUDs) are among the top contributors to the global burden of disease[1] because of their high prevalence and inaccessibility of effective treatments.[2,3] Cannabis products are increasingly becoming available for medical use and gaining attention as alternative treatments for mental disorders and SUDs. Phytocannabinoids, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol, are potential therapeutic agents as they have been

Research in context

Evidence before this study

We searched PubMed and grey literature from database inception to Aug 14, 2025, for reviews of cannabinoids for the treatment of mental disorders and substance use disorders (SUDs) using the Medical Subject Headings (MeSH) terms (("medical cannabis" [All Fields] OR "medical marijuana" [All Fields] OR "cannabinoids" [All Fields]) AND ("mental health" [All Fields] OR "substance related disorders" [All Fields]) AND ("review" [All Fields])). This search led to 634 results, of which 16 were relevant reviews where the mental disorder or SUD was the primary indication that cannabinoids were used to treat. Of these, few reviews included all mental disorders and SUDs (n=6), conducted a meta-analysis (n=4), or thoroughly evaluated the quality of evidence (n=2). All studies agreed that there was mixed or sparse evidence for the efficacy of these medicines for the treatment of mental disorders or SUDs.

Added value of this study

Our study represents, to our knowledge, the largest and most comprehensive systematic review and meta-analysis of evidence from randomised controlled trials on the efficacy and safety of cannabinoids for the treatment of mental disorders and SUDs. We included all mental disorders and SUDs where they were the primary indication for treatment, pooled data on remission from disorder and change in symptoms, health-related outcomes, and adverse events where possible. We concluded that a mix of cannabidiol and delta-9-tetrahydrocannabinol reduced cannabis withdrawal symptoms and quantity of cannabis use among those with cannabis use disorder, and a reduction in tic severity among those with tic or Tourette's Syndrome. Cannabinoids led to an increase in sleep time among those with insomnia and a reduction in autistic traits among those with autism spectrum disorder. There was no benefit of cannabinoids for the treatment of anxiety, anorexia nervosa, psychotic disorders, post-traumatic stress disorder, and opioid use disorder. There was insufficient data for ADHD, bipolar disorder, obsessive-compulsive disorder, and tobacco use disorder. Cannabinoids were associated with a greater risk of all-cause adverse events compared with placebo, but no higher odds of serious adverse events or study withdrawal. This Article systematically evaluates the efficacy and safety of cannabinoids for some of the most common indications that they are used to treat, providing clarity during a time of expanding clinical use. Sleep issues, post-traumatic stress disorder, and depression are some of the leading indications that cannabinoids are used to treat, yet there were only four randomised controlled trials for sleep issues, three for post-traumatic stress disorder, and none for depression that examined cannabinoid efficacy.

Implications of all the available evidence

Cannabinoids are increasingly being authorised for the treatment of mental disorders and SUDs, yet our review shows little evidence of efficacy. There is a substantial gap between clinical use and available evidence. It is concerning that the use of these treatments could delay or replace the use of more effective therapies. There is a crucial need for improved study design that includes larger and more representative participant samples.

shown to modulate the endocannabinoid system, non-endocannabinoid receptors, and neurotransmitters that play a role in mental disorders and SUDs.[4–6] Consequently, cannabinoid medicines are now authorised for the treatment of mental disorders and SUDs in the USA, Canada, and Australia.[7,8] 27% of the estimated population aged 16–65 years in the USA and Canada reported ever using cannabis for medical purposes, half of which were for managing their mental health.[8] In Australian markets, where cannabinoid medicines have been legalised more recently, over one million applications have been approved for the use of these medicines and mental disorders make up six of the top ten most common indications for which they are prescribed.[7]

A 2016 review on the efficacy of cannabinoids for mental disorders found that significant benefits were sparse, risk of harm was high, and evidence was predominantly based on observational studies or randomised controlled trials (RCTs) where mental disorders were secondary to a primary health condition (eg, chronic pain).[9] When focusing on RCT evidence, anxiety symptoms were the only outcome that were reduced by cannabinoids compared with placebo, but the quality of evidence was low and the risk of adverse events was high (number needed to treat to harm [NNTH] of seven). Since then, several systematic reviews of RCTs have concluded that there is mixed or sparse evidence for the efficacy of cannabinoids for mental disorder and SUD outcomes.[10–14] There were no meaningful benefits found for most psychiatric disorders, aside from promising evidence for cannabidiol as an adjunctive treatment for schizophrenia. However, few reviews included evidence for the treatment of all mental disorders and SUDs as the primary indication,[10,11] conducted meta-analyses,[11,14] critically evaluated the risk of bias and quality of evidence,[13,14] or examined the evidence according to the type of cannabinoid.[11,14]

Considering the recent rise in the use of cannabinoids for the treatment of mental disorders and SUDs, there is a need to examine the current state of evidence. Therefore, the aim of this systematic review and meta-analysis is to synthesise and assess the quality of RCT evidence on the efficacy and safety of cannabinoids for the treatment of any mental disorders and SUDs.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched Ovid MEDLINE, PsychINFO, Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, and Embase for peer-reviewed RCTs evaluating the efficacy of plant-based and pharmaceutical cannabinoids in reducing or treating mental disorders and SUDs. The search was limited to articles published from Jan 1, 1980, to May 13, 2025, with no restriction on language. Search strategies included terms related to cannabis, clinical trial, mental disorders, and SUDs (appendix pp 9–16). Ongoing or unpublished studies were searched on ClinicalTrials.gov, EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry. A manual search of reference lists and relevant systematic reviews was also conducted by JW, AL, MG, JL, ZB, OD, or PM to capture relevant articles, and we consulted experts in the field to identify other studies not found through these searches. Two reviewers (JW, AL, MG, JL, ZB, OD, or PM) independently examined titles and abstracts using the web-based screening platform Covidence. Relevant articles were screened in full and assessed for inclusion independently by two reviewers (JW, AL, MG, JL, ZB, OD, or PM). Disagreement between reviewers was resolved either by discussion or a third reviewer (ES).

See **Online** for appendix

For the **Covidence screening platform** see www.covidence.org

Studies eligible for inclusion were RCTs testing the efficacy and safety of any form of cannabinoids for mental disorders or SUDs among participants of any age and in any setting. The systematic review considered studies that evaluated plant-based or pharmaceutical cannabinoids, or both, administered with the intention of reducing symptoms or improving outcomes associated with mental disorders and SUDs. The exclusion criteria included any non-RCTs or any non-clinical samples as these methodologies do not meet the gold standard for clinical decision making.[15] Reference groups were those administered placebo, active medications, waitlist controls, or other interventions. Primary outcomes included remission from the primary mental disorder or SUD and changes in symptoms. Secondary outcomes included changes in health-related outcomes, including global functioning, cardiovascular measures, weight, and sleep. We examined all-cause adverse events (eg, nausea) and serious adverse events (eg, psychotic episode), as well as study withdrawals. Adverse event data were extracted according to how they were categorised in the trial and were not recoded in this study. The study was registered with PROSPERO (CRD42023392718).[16]

Although we acknowledge the various language terms used to describe autism, in this Article we refer to autistic traits.

Data analysis

Data were extracted independently by two reviewers (JW, AL, MG, JL, ZB, OD, or PM) using a prepiloted data extraction form in Microsoft Excel. Data were collected on the details of the population, intervention, comparison (ie, control), outcomes of significance to the mental disorder or SUD, or both, study design (eg, parallel or crossover design), cannabinoid dose and route of administration, placement in the therapeutic hierarchy (eg, if administered with co-intervention), and adverse events and study withdrawals. In cases where multiple articles provided data on a single RCT, all available data were extracted and duplicate data were removed. Supplementary information and study protocols were extracted and authors were contacted when relevant data were not provided. Hozo and colleagues' method[17] was used to calculate standard deviation when median, range, and sample sizes were provided. When multiple analyses were reported (eg, intention to treat, available case, or per protocol), the most conservative figures were extracted with a preference for intention to treat. Review Manager (version 5.4) was used for all analyses.

Risk of bias was assessed using the Cochrane risk of bias tool 2.0.[18] The assessment included indicators of bias arising from randomisation, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. An assessment of bias arising from conflicts of interest and source of funding was also incorporated. Risk of bias assessments were completed independently by two reviewers (JW, AL, or OD). Disagreement between reviewers was resolved either by discussion or a third reviewer (ES).

The GRADE framework[19] was used to assess the quality of evidence for each outcome based on five domains: risk of bias, indirectness of evidence, inconsistency of results, imprecision, and publication bias. GRADE assessments were conducted by one reviewer and checked by a second reviewer, with disagreement resolved by discussion or through a third reviewer (JW, OD, or PM). A high-quality rating indicates greater certainty that the true effect is similar to the estimated effect, whereas a low-quality rating indicates that the true effect is likely to be different from the estimated effect.

For the meta-analysis, outcomes specific to each mental disorder or SUD were combined where possible with the use of random-effects models. Continuous outcomes were pooled as standardised mean differences (SMDs) and dichotomous outcomes as odds ratios (ORs). To synthesise studies with multiple experimental groups (eg, 20 mg and 40 mg of cannabidiol), we analysed each group separately and divided the comparison group by the number of intervention groups. Where sufficient data were available, subgroup analyses were conducted to explore outcomes based on the cannabinoid (ie, cannabidiol, THC, or a combination of both). Adverse events were meta-analysed according to each mental disorder or SUD.

Heterogeneity was assessed by examining the I^2 statistic and associated p value, whereby a p value of less than 0·10 or an I^2 statistic of at least 50% indicated significant statistical heterogeneity. Sensitivity analyses (leave one out method) were conducted to determine the degree of heterogeneity based on risk of bias and key study characteristics, such as sample type, setting, dose, and treatment length. We included people with related lived experience in the study design and implementation.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The combined search identified 5774 titles, of which 343 were duplicates. The remaining 5431 were screened by title and abstract (figure 1). Of these, 5292 were deemed irrelevant and 139 were assessed in full to determine eligibility. At full-text screening, 81 were deemed irrelevant (appendix pp 17–24), resulting in 58 eligible titles. After, a further four titles were identified through reference lists, resulting in a total of 62 titles contributing data from 54 unique trials (appendix pp 25–27). We also identified 14 ongoing trials through clinical trials registries that could not be included in the current synthesis (appendix p 28).

The characteristics of the 54 included studies comprising 2477 participants (1713 [69%] male, 764 [31%] female) are summarised in tables 1 and 2. Cannabinoids were most commonly used to treat cannabis use disorder (n=12), followed by psychotic disorders (n=8) and anxiety disorders (n=6). A small number of studies were found for tic or Tourette's syndrome (n=5), opioid use disorder (n=4), insomnia (n=4), cocaine use disorder (n=3), PTSD (n=3), anorexia nervosa (n=2), autism spectrum disorder (n=2), and obsessive compulsive disorder (OCD; n=2). There was one study each for ADHD, bipolar disorder, and tobacco use disorder. Details of each study are provided in the appendix (pp 29–42).

Most studies were parallel group design (n=32), had a median sample of 31·5 participants (IQR 16·5–57·8), a median age of 33·3 years (28·1–38·1), and a median of 18·0 (70·7%) males (52·0–82·3) and 10·5 (29·4%) females (17·7–48·0). 11 studies were multidose studies. The most common cannabinoid was cannabidiol (n=24), followed by THC (n=18) and a combination of THC and cannabidiol (n=12). Cannabinoids were commonly administered as the primary treatment in the therapeutic hierarchy (n=46) for an average treatment duration of 4·98 weeks (SD 4·41).

Where meta-analysis was possible, figure 2 shows findings for the primary outcomes for each condition alongside their GRADE assessment. Figure 3 shows findings for adverse events and study withdrawals for each condition alongside their GRADE assessment. Results are presented by disorder type.

Overall, 24 (44%) of 54 studies were rated as at high risk of bias, 20 (37%) raised some concerns, and ten (18%) were of low risk (appendix pp 43–44). We also assessed bias related to conflicts of interest. Although 27 (50%) studies were rated as low risk in conflicts of interest, 16 (30%) raised some concerns and 11 (20%) were at high risk, primarily because of author industry involvement and financial relationships and the unclear roles of sponsors in study design and reporting.

12 studies[20–31] (678 participants) examined the efficacy of cannabinoids among people with cannabis use disorder (table 2; appendix pp 51–54). Random effects meta-analysis revealed a significant reduction in cannabis withdrawal symptoms among those receiving cannabinoid compared with controls (SMD –0·70, 95% CI –1·32 to –0·09; GRADE very low certainty; figure 2). Subgroup analyses revealed that this effect was significant for studies that administered pharmaceutical-grade mixed cannabidiol and THC (nabiximols) compared with placebo (–0·29,

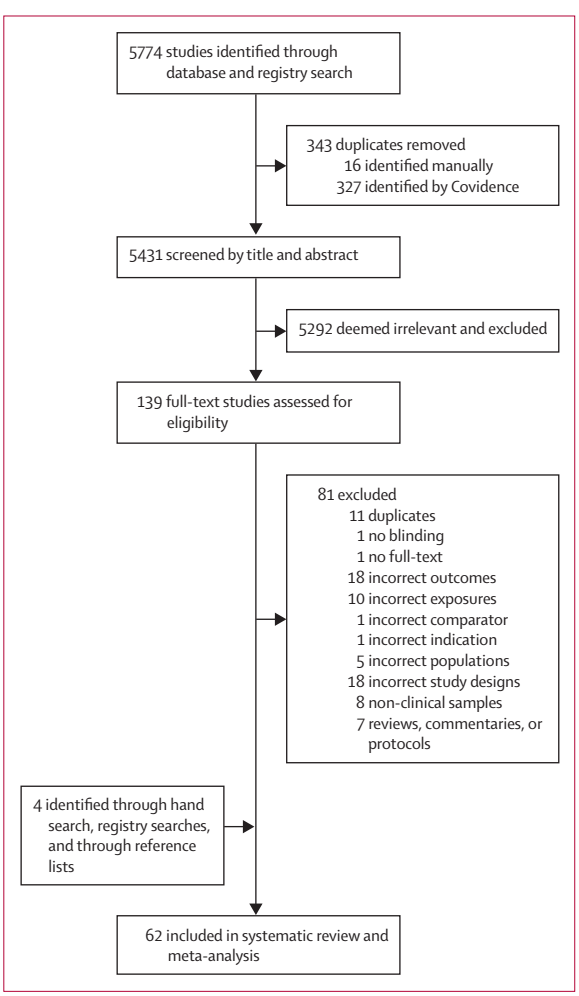


Figure 1: **Study selection**

	Psychotic disorders (n=8)	Anxiety disorders (n=6)	Tic or Tourette's syndrome (n=5)	Insomnia (n=4)	PTSD (n=3)	Anorexia nervosa (n=2)	ASD (n=2)	OCD (n=2)	ADHD (n=1)	Bipolar disorder (n=1)
Region										
Asia	0	2	0	1	0	0	1	0	0	0
North America	2	1	1	0	2	1	0	2	0	0
South America	1	2	0	0	1	0	1	0	0	1
Europe	5	1	3	0	0	1	0	0	1	0
Oceania	0	0	1	3	0	0	0	0	0	0
Year of study										
1980–89	0	1	0	0	0	1	0	0	0	0
1990–99	0	0	0	0	0	0	0	0	0	0
2000–09	1	0	2	0	0	0	0	0	0	0
2010–19	4	3	0	0	1	1	0	0	1	0
2020–25	3	2	3	4	2	0	2	2	0	1
Participant characteristics										
Total number	290	352	168	137	123	35	210	64	30	35
Median number	31·5	32	22	34	33	17·5	105	32	30	35
Age, years	35·1 (27·7–44·5)	29·0 (24·0–37·1)	34·0 (32·0–37·2)	46·1 (38·4–50·0)	43·6 (38·4–44·2)	28·5 (NA)	9·8 (NA)	28·8 (NA)	37·9 (NA)	43·9 (NA)
Sex										
Female	84 (29·0%)	126 (35·8%)	39 (23·2%)	93 (67·9%)	33 (26·8%)	35 (100%)	38 (18·1%)	46 (71·9%)	11 (36·7%)	24 (68·6%)
Male	206 (71·0%)	226 (64·2%)	129 (76·8%)	44 (32·1%)	90 (73·2%)	0 (0%)	172 (81·9%)	18 (28·1%)	19 (63·3%)	11 (31·4%)
Place in therapeutic hierarchy										
Primary	3	5	5	4	3	2	1	2	1	0
Secondary	5	1	0	0	0	0	1	0	0	1
Single dose or multidose										
Single	7	6	4	4	2	2	1	1	1	1
Multi	1	0	1	0	1	0	1	1	0	0
Route of administration										
Oral	6	6	4	4	2	2	2	1	1	1
Smoked	1	0	0	0	1	0	0	1	0	0
Vapourised	0	0	1	0	0	0	0	0	0	0
Intravenous	1	0	0	0	0	0	0	0	0	0
Inhaler	0	0	0	0	0	0	0	0	0	0
Treatment duration, weeks	3·1 (0·1– 6·0)	4·9 (0·1–13·0)	5·1 (0·1–13·0)	2·5 (2·0–4·0)	4·3 (1·0–7·0)	3·0 (2·0–4·0)	12·0 (12·0)	5·1 (0·1–10·0)	6·0 (NA)	12·0 (NA)
Cannabinoid classification										
THC only	1	1	3	0	2	2	0	1	0	0
CBD only	7	5	1	2	2	0	0	0	0	1
Combined THC and CBD	0	0	3	2	1	0	2	1	1	0
Longest follow-up										
≤1 day	2	2	2	0	0	0	0	1	0	0
≤1 week	1	0	0	0	1	0	0	0	0	0
≤1 month	2	2	0	4	0	1	0	0	0	0
>1 month	3	2	3	0	2	1	2	1	1	1

Data are n, median (IQR), percentage, mean, or range. Psychotic disorders include schizophrenia and other psychotic disorders. ADHD=attention-deficit hyperactivity disorder. ASD=autism spectrum disorder. CBD=cannabidiol. NA=not applicable. OCD=obsessive compulsive disorder. PTSD=post-traumatic stress disorder. THC=delta-9-tetrahydrocannabinol.

Table 1: **Study characteristics for the treatment of mental disorders**

–0·57 to –0·02), but not in studies when THC or cannabidiol were administered on their own (appendix p 58). Sensitivity analysis showed that when removing studies with high risk of bias, the overall effect on withdrawal symptoms was no longer significant (–0·84, –1·75 to 0·06). Random effects meta-analysis revealed a significant reduction in cannabis use (assessed typically by self-report) after treatment with cannabinoid compared with control (–0·74, –1·18 to –0·30; GRADE low certainty; figure 2). Subgroup analysis revealed that this was significant for studies measuring weekly grammes of cannabis use (–1·00, –1·69 to –0·30), but not frequency of use (–0·48, –1·07 to 0·11; appendix p 60). Random effects meta-analysis showed no significant effect on cannabis craving (–0·14, –0·39 to 0·10), cannabis problems (defined as health, social, and psychological problems arising from cannabis use; –0·14, –0·49 to 0·21), or cannabis abstinence (OR 1·26, 95% CI 0·79 to 2·01) between the cannabinoid and comparison groups (figure 2). Random effects meta-analysis revealed no significant effect on experiencing an adverse event (1·07, 0·75 to 1·53), experiencing a serious adverse event (1·31, 0·28 to 6·17), or study withdrawal (0·83, 0·58 to 1·17) between cannabinoid and comparison groups (figure 3). Results for secondary health outcomes associated with each mental disorder and SUD are presented in the appendix (pp 45–57).

Eight studies[32–39] (290 participants) examined the efficacy of cannabinoids (predominantly cannabidiol) in people with schizophrenia and other psychotic disorders (table 1). Random effects meta-analysis revealed no significant effect on Positive and Negative Syndrome Scale (PANSS) scores (SMD –0·14, 95% CI –0·39 to 0·11), PANSS positive scores (–0·13, –0·38 to 0·12), PANSS negative scores (–0·00; –0·25 to 0·25), or general symptoms (–0·12, –0·46 to 0·22) between cannabinoid and comparison groups (figure 2). Random effects meta-analysis revealed no significant effect of cannabinoids on adverse events (OR 0·87, 95% CI 0·39 to 1·96), serious adverse events (0·99, 0·10 to 9·92), or study withdrawals (1·05, 0·46 to 2·41; figure 3).

Six studies[40–45] (352 participants) examined the efficacy of cannabinoids among people with an anxiety disorder (table 1), three of which focused on symptoms of social anxiety disorder,[40,41,45] whereas the remaining studies treated general symptoms of anxiety.[42–44] Random effects meta-analysis revealed no significant effect on anxiety symptoms at longest follow-up between cannabinoid and comparison groups (SMD –1·88, 95% CI –4·79 to 1·03; figure 2). Random effects meta-analysis revealed no significant effect of cannabinoids on adverse events (OR 1·48, 95% CI 0·37 to 5·86) or study withdrawal (1·42, 0·11 to 18·73), compared with placebo (figure 3). No studies reported serious adverse events.

Five studies[46–50] (168 participants) examined the efficacy of cannabinoids among people with tic or Tourette's syndrome (table 1). Random effects meta-analysis revealed an overall significant reduction in tic severity following cannabinoids compared with placebo (SMD –0·62, 95% CI –0·92 to –0·32; GRADE very low; figure 2). Subgroup analysis showed that although there was a significant improvement when mixed cannabidiol and THC was administered (–0·68, –1·03 to –0·34), there was no significant improvement when cannabidiol alone (–0·24, –1·55 to 1·07) or THC alone (–0·47, –1·17 to 0·22;

	Cannabis use disorder (n=12)	Opioid use disorder (n=4)	Cocaine use disorder (n=3)	Tobacco use disorder (n=1)
Region				
Asia	0	0	0	0
North America	9	4	1	0
South America	0	0	2	0
Europe	1	0	0	1
Oceania	2	0	0	0
Year of study				
1980–89	0	0	0	0
1990–99	0	0	0	0
2000–09	1	0	0	0
2010–19	10	3	0	1
2020–25	1	1	3	0
Participant characteristics				
Total number	678	132	199	24
Median number	32	31	78	24
Age, years	32·5 (27·0–35·1)	41·6 (34·7- 47·4)	39·4 (NA)	28·0 (NA)
Sex				
Female	165 (24·3%)	28 (21·2%)	30 (15·1%)	12 (50·0%)
Male	513 (75·7%)	104 (78·8%)	169 (84·9%)	12 (50·0%)
Place in therapeutic hierarchy				
Primary	12	4	3	1
Secondary	0	0	0	0
Single dose or multidose				
Single	8	2	3	1
Multi	4	2	0	0
Route of administration				
Oral	12	4	3	0
Smoked	0	0	0	0
Vapourised	0	0	0	0
Intravenous	0	0	0	0
Inhaler	0	0	0	1
Treatment duration, weeks	5·9 (0·7–12·0)	3·4 (0·1–8·0)	7·9 (1·4–13·1)	1·0 (NA)
Cannabinoid classification				
THC only	7	2	0	0
CBD only	1	2	3	1
Combined THC and CBD	4	0	0	0
Longest follow-up				
≤1 day	1	1	0	0
≤1 week	2	1	0	0
≤1 month	3	0	1	1
>1 month	6	2	2	0

Data are n, median (IQR), percentage, mean, or range. CBD=cannabidiol. NA=not applicable. THC=delta-9-tetrahydrocannabinol.

Table 2: **Study characteristics for the treatment of substance use disorders**

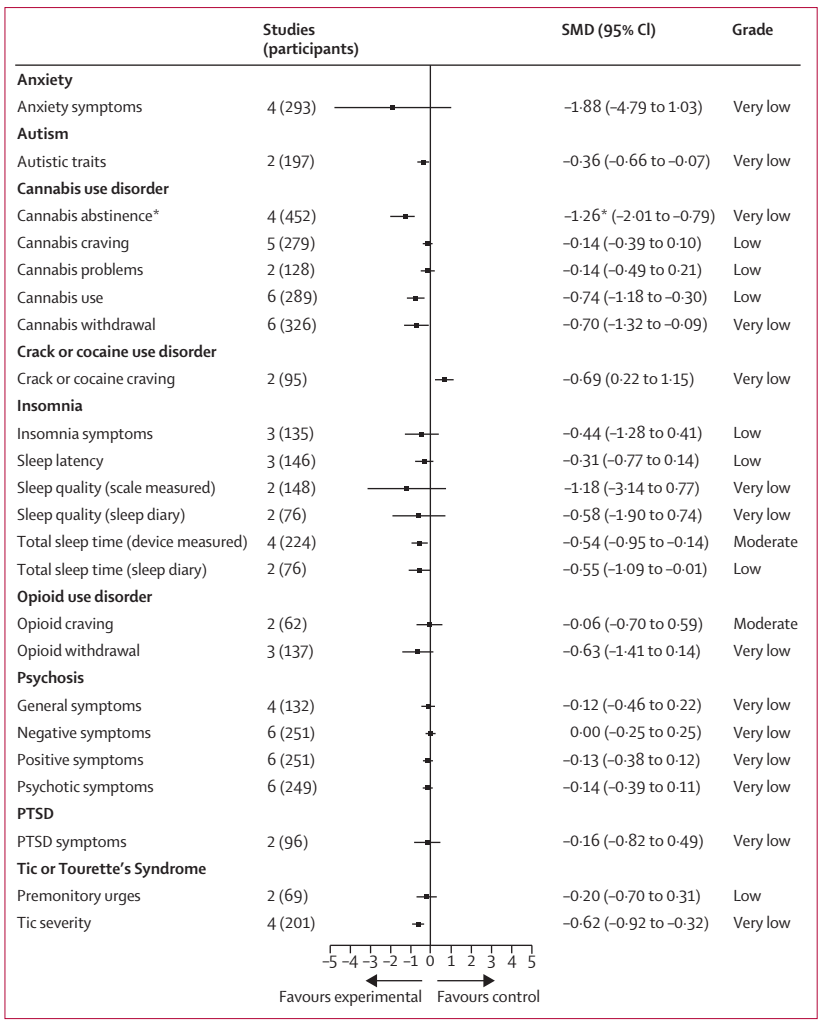


Figure 2: **Summary of meta-analyses on the efficacy of cannabinoids for the treatment of mental disorder and substance use disorder primary outcomes**

Sleep time and sleep quality scores are presented in reverse to reflect favouring the experimental group. PTSD=post-traumatic stress disorder. SMD=standardised mean difference. *Odds ratio; result is not significant.

appendix p 83) was administered. Random effects meta-analysis revealed no significant effect of cannabinoids on premonitory urges (–0·20, –0·70 to 0·31) compared with placebo (figure 2). Random effects meta-analysis revealed significantly greater odds of adverse events among the cannabinoid group compared with the placebo group (OR 4·93, 95% CI 1·80 to 13·48; figure 3). One study reported two serious adverse events,[48] with one in the cannabinoid group (n=64) and one in the placebo group (n=33). Random effects meta-analysis revealed no significant effect of cannabinoids on study withdrawal compared with placebo (0·96, 0·42 to 2·22; figure 3).

Four studies[51–54] (132 participants) examined the efficacy of cannabinoids among people with an opioid use disorder (table 2). Random effects meta-analysis revealed no significant effect on withdrawal symptoms (SMD –0·63, 95% CI –1·41 to 0·14) or opioid craving (–0·06, –0·70 to 0·59; figure 2). There was no significant difference in all-cause adverse events between cannabinoid and placebo conditions (OR 2·12, 95% CI 0·56 to 7·97; figure 3). One study reported serious adverse events, one in the cannabinoid group (n=27) and two in the placebo group (n=11).[51] In the same study, 26 participants withdrew from the cannabinoid group and 13 from the placebo group.

Four studies[55–58] (137 participants) examined the efficacy of cannabinoids among people with insomnia (table 1). Random effects meta-analysis revealed no overall significant effect on insomnia symptoms (SMD –0·44, 95% CI –1·28 to 0·41; figure 2), but a significant increase in sleep time when measured via an electronic device (0·54, 0·14 to 0·95; GRADE moderate certainty) and a self-reported sleep diary (0·55, 0·01 to 1·09; GRADE low certainty; figure 2). However, sleep time measured via electronic device was no longer significant in subgroup analyses when studies of high risk of bias were excluded (0·44; –0·10 to 0·98; appendix p 96). Random effects meta-analysis revealed no significant effect of cannabinoids on the measure of sleep quality as recorded by a scale (–1·18, –3·14 to 0·77) or sleep diary (–0·58, –1·90 to 0·74; figure 2). There was no significant effect on sleep latency compared with placebo (–0·31, –0·77 to 0·14; figure 2). Some differences in sleep outcomes were identified between the use of cannabidiol and mixed cannabidiol and THC, but these were highly uncertain because there was only one study per subgroup (appendix pp 95–99). Random effects meta-analysis revealed significantly greater odds of adverse events among the cannabinoid group compared with the placebo group (OR 11·04, 95% CI 4·37 to 27·92; figure 3). There were high rates of adverse events in the cannabinoid group, with the most common being dry mouth, nausea, diarrhoea, and dizziness. Two serious adverse events were reported by one study,[57] both participants were in the cannabinoid group (n=29). Random effects meta-analysis revealed no effect of cannabinoids on study withdrawals compared with placebo (2·33, 0·76 to 7·18; figure 3).

Three studies[59–61] (199 participants) examined the efficacy of cannabinoids among people with cocaine use disorder (table 2). Random effects meta-analysis revealed a significant increase in cocaine craving in the cannabinoid group compared with the control group (SMD 0·69, 95% CI 0·22–1·15; GRADE very low certainty; figure 2). There were significantly greater odds of experiencing an adverse event in the cannabinoid group compared with the placebo group (OR 3·76, 95% CI 1·70–8·33; figure 3). One study reported one serious adverse event[60] in the placebo group (38 participants). All three studies reported participant withdrawals. Random effects meta-analysis revealed no significant effect of cannabinoids on study withdrawal compared with placebo (0·73, 0·39–1·38; figure 3).

Three studies[62–64] (123 participants) examined the efficacy of cannabinoids among people with PTSD

(table 1). Random effects meta-analysis revealed no significant effect on PTSD symptoms at longest follow-up between the cannabinoid and comparison groups (SMD –0·16, 95% CI –0·82 to 0·49; figure 2). There was no significant effect of cannabinoids on adverse events compared with the placebo group (OR 1·00, 95% CI 0·29 to 3·48; figure 3). One study reported data on serious adverse events and study withdrawal. Three serious adverse events and six study withdrawals were recorded in the cannabinoid groups, whereas none were recorded in the control group.

Two studies[65,66] (35 participants) examined the efficacy of cannabinoids among people with anorexia nervosa (table 1). Qualitative analysis revealed no significant difference in mean weight[66] or average daily physical activity between treatment and comparison groups.[65] Neither study provided sufficient data to report on withdrawals or adverse events.

Two studies[67,68] (210 participants) examined the efficacy of cannabinoids in people with autism spectrum disorder (table 1). Random effects meta-analysis revealed a significant reduction in autistic traits, as measured by the Social Responsiveness Scale and Autism Treatment Evaluation Checklist, at longest follow-up in the cannabinoid group compared with the placebo group (SMD –0·36, 95% CI –0·66 to –0·07; GRADE very low certainty; figure 2). However, when examined based on cannabinoid (mixed cannabidiol and THC *vs* cannabidiol alone) in subgroup analysis, neither subgroup showed a significant reduction (appendix p 110). There were insufficient data to meta-analyse adverse events and study withdrawals, but narrative synthesis identified similar rates of these outcomes between treatment and comparison groups (appendix pp 46–47).

Two studies[69,70] (64 participants) examined the efficacy of cannabinoids among people with OCD (table 1). Qualitative analysis revealed there was no significant difference in body-focused repetitive behaviours or skin picking,[69] or general OCD symptoms[70] between cannabinoid and placebo groups. One study reported adverse events and study withdrawals;[69] there were 16 all-cause adverse events in the cannabinoid group (n=25) compared with seven in the control group (n=25) and 11 participants withdrew from the cannabinoid group compared with nine from the placebo group.

One study[71] each examined the efficacy of cannabinoids versus control for ADHD (30 participants), bipolar disorder[72] (35 participants), and tobacco use disorder[73] (24 participants; tables 1 and 2). No significant differences were found for any outcome for ADHD, bipolar disorder, or tobacco use disorder. Insufficient data were available to analyse adverse events or study withdrawals. Full details per study are provided in the appendix (pp 45–47).

Across all mental disorders and SUDs, 28 studies provided sufficient data for all-cause adverse events to be meta-analysed.[21,24–27,29–32,35,37,39,43,44,48–52,57–60,63,64,68,69,71] Random effects meta-analysis revealed significantly greater odds of adverse events in the cannabinoid group than in the placebo group (OR 1·75, 95% CI 1·25–2·46; figure 3). Subgroup analysis showed that this effect was significant among studies that administered combined cannabidiol and THC (eight studies; 2·60, 1·11–6·08) and cannabidiol alone (12 studies; 1·66, 1·01–2·72), but this effect was not significant for THC alone (ten studies; 1·41, 0·96–2·07; appendix p 111). Overall, it is estimated that one additional participant would experience an adverse event for every seven (95% CI 5·4–10·8) participants treated with cannabinoids (NNTH 7). 12 studies provided sufficient data on serious adverse events for a meta-analysis.[25–27,35,37,48,51,57,60,63,67,71] Random effects meta-analysis revealed no significant effect of cannabinoids on serious adverse events compared with placebo (OR 1·12, 95% CI 0·51–2·47; figure 3). Across all mental disorders and SUDs, 30 studies provided sufficient data for study withdrawals to be meta-analysed.[20,21,24–27,30,32,35–37,39,44,45,47,48,50,51,55–61,63,67,69,71,72] Random effects meta-analysis revealed no significant effect of cannabinoids on study withdrawals compared with placebo (0·91, 0·72–1·14; figure 3). Subgroup analysis showed that this effect was not significant for cannabidiol, THC, or mixed cannabidiol

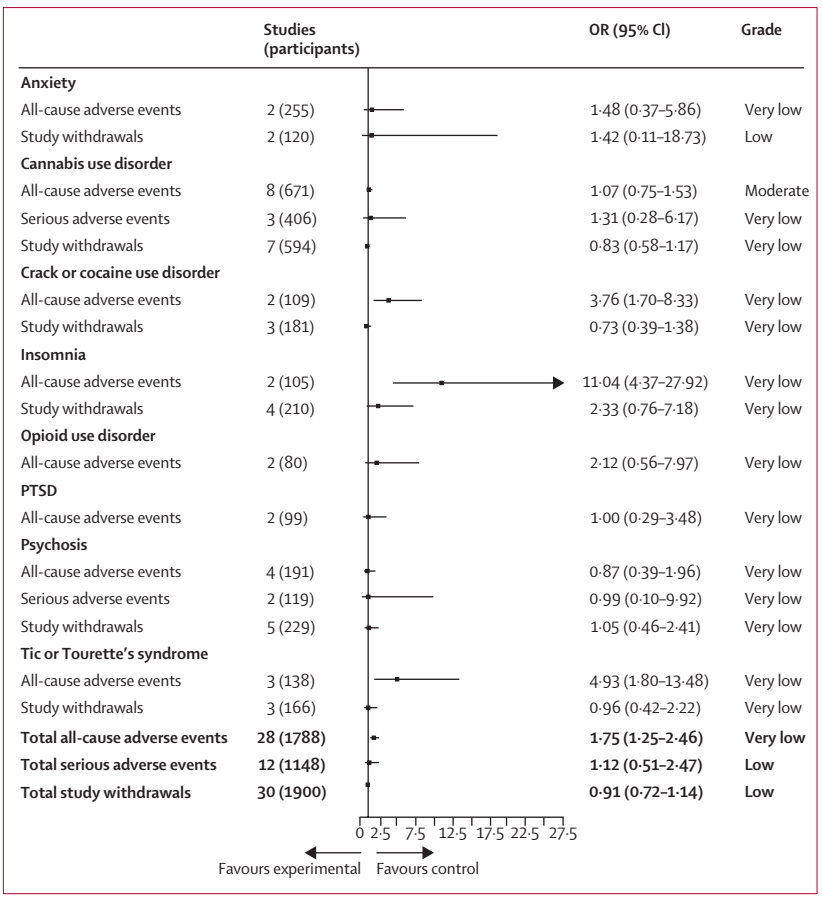


Figure 3: **Summary of meta-analysis on the safety of cannabinoids for the treatment of mental disorders and substance use disorders**

OR=odds ratio. PTSD=post-traumatic stress disorder.

and THC conditions compared with placebo (appendix p 113).

Discussion

To date, to the best of our knowledge, this is the largest and most comprehensive systematic review and meta-analysis of evidence from RCTs on the efficacy and safety of cannabinoids for the primary treatment of mental disorders and SUDs. Meta-analysis found no benefit of cannabinoids for opioid use disorder, tobacco use disorder, cocaine use disorder, bipolar disorder, anxiety, ADHD, psychotic disorders, PTSD, OCD, or anorexia nervosa. Cannabinoids were associated with a reduction in withdrawal symptoms and cannabis use among those with a cannabis use disorder and in a reduction in autistic traits among those with autism spectrum disorder. However, according to GRADE, there was very low certainty in the evidence for a reduction in autistic traits, and both studies contributing data to this outcome exhibited a high risk of bias. There was also a reduction in insomnia symptoms and some evidence of an improvement in sleep time. We identified a reduction in tic severity among those receiving cannabinoids, but only for those administered cannabidiol and THC in combination.

Those who were administered cannabinoids experienced significantly more adverse events compared with those who received placebo, but serious adverse events and study withdrawals did not differ between groups. For every seven participants treated with cannabinoids, one experienced an adverse event compared with placebo. Despite the increase in the number of RCTs since earlier reviews,[9–14] the quality of evidence remained low. To improve the quality of the evidence base, studies must be transparent in their reporting of all primary outcomes according to preregistered study protocols and minimise the involvement of cannabinoid-related industry funding. Furthermore, larger and more representative study samples must be used to provide more valid and precise estimates.

Cannabinoids are increasingly being permitted for the treatment of mental disorders and SUDs,[7,8,74] but there was little evidence for its efficacy in the current review. Findings from the USA and Canada suggest that sleep problems, anxiety, depression, PTSD, and SUDs are among the leading reasons people report using medical cannabis.[8] These are also among the most common indications according to prescription application approval data in Australia[7] and a small survey dataset in the UK.[74] Yet in this Article, cannabinoids had no significant effect on primary outcomes for treating anxiety, PTSD, and all SUDs except for cannabis use disorder. There were no RCTs assessing cannabis for the treatment of depression.

The regulatory expansion of cannabinoids has been argued to have been based on the perception of a low risk profile rather than on good evidence of effectiveness.[75] Our review provides some support for this assertion considering that there was no greater risk of serious adverse events or withdrawals between cannabinoid and placebo groups. However, it is important to note that most included studies used registered cannabinoids, such as Sativex (Jazz Pharmaceuticals, Dublin, Ireland), rather than unregistered high-THC products such as those commonly found in Australian,[7] US,[76] and Canadian[77] markets. These products could increase the risk of developing cannabis use disorder, among other long-term harms that are not captured during an RCT. Given the absence of evidence of efficacy, it is of concern that the use of cannabinoids could delay or replace the use of known effective therapies, such as cognitive behavioural therapies, which have shown large effect sizes in treating depressive and anxiety disorders.[78]

However, there were some promising findings for cannabinoids as a treatment for cannabis use disorder, autism spectrum disorder, insomnia, and tic or Tourette's syndrome. Relative to the control condition, cannabinoid treatments showed the strongest effect on improving cannabis abstinence, with smaller effects on reducing cannabis use and cannabis withdrawal, reducing autistic traits, improving sleep time as measured by an electronic device, and reducing tic severity. It might be expected that cannabinoids would be effective in reducing cannabis withdrawal and use, acting as a replacement for non-medical cannabis. Interestingly, most of these beneficial findings were attributed to the administration of mixed cannabidiol and THC formulations. However, there was low to very low level of certainty in these findings. The only outcome where cannabinoids were beneficial with a moderate level of certainty was improved sleep time according to a device measurement among those with insomnia. Although few studies contributed data to the synthesis of autism, insomnia, and tic or Tourette's syndrome outcomes, these findings are encouraging given the scarcity of effective and safe pharmacological treatment options for these conditions. To date, there are no approved medications available for the treatment of cannabis use disorder and several commonly prescribed treatments for insomnia carry notable risks, such as dependence and next-day side-effects.[79] Overall, the findings of this Article support further investigation of the therapeutic use of cannabinoids for these conditions, with improved study designs that include larger and more representative participant samples.

The scarcity of evidence of efficacy constrasts with dramatic increases in use within some regions,[7,8,74] which suggests there should be greater regulatory oversight in the use of cannabinoids as medicines. Such regulations are particularly important in contexts where health practitioners are financially incentivised to recommend cannabinoids to patients. There are consistent claims that health workers feel unprepared when discussing these treatments.[80] We recommend that health workers

be required to complete training on the risk–benefit profile of these medicines. Authorisers of medical cannabis use should have access to a continuously updated database that presents and appraises the evidence according to indication and cannabinoid product. Furthermore, it might be necessary to reshape public health messaging about these medicines to minimise negative or positive attitudes traditionally aimed at non-medical use, both of which can cause expectancy or placebo effects.[81] People often report self-treating their health conditions with non-medical cannabis products.[82] However, this study shows that only a small number of cannabis products and dose forms have been examined for their efficacy and safety. Public messaging around medicinal cannabinoids should emphasise the importance of tested products.

Our study has some limitations. We focused on outcomes at the longest follow-up, whereas some studies might have observed varying effects at multiple time points. We argue the longest follow-up to be the most clinically relevant, and the combination of multiple time points for each study risks introducing unit-of-analysis error.[83] Subgroup analysis according to cannabinoid type was limited by the small number of studies and their small sample sizes.[84] There might have been gender or sex differences in the efficacy and safety of cannabinoids, but this analysis was not provided by most studies. Observational datasets were not included: although they could shed some light on the efficacy of cannabinoids as a treatment for these conditions, potential biases are more likely to arise in these study designs, and they cannont establish a causal relationship.[85]

Despite the increasing use of cannabinoids to treat mental disorders and SUDs, we found relatively weak evidence that they were beneficial compared with placebo in most conditions. There was some evidence that supported the use of cannabinoids, typically mixed cannabidiol and THC, in the relief of symptoms related to cannabis use disorder, insomnia, and tic or Tourette's syndrome and autism spectrum disorder, but the quality of evidence was low. There is a crucial need for RCTs with larger and more representative samples. It is concerning that the use of these treatments could delay or replace the use of more effective therapies. Overall, given the scarcity of evidence for efficacy and greater risk of all-cause adverse outcomes, the routine use of these medicines for mental disorders and SUDs is rarely justified.

Contributors

JW and ES conceptualised the Article. JW, ES, OD, AL, PM, ZB, and DD had access to the data and were involved in data extraction and analysis. All authors were involved in editing and writing the manuscript. JW and ES had the final decision to submit the manuscript. All authors had access to the study data and had final responsibility for the decision to submit the manuscript for publication. JW and ES accessed and verified the data underlying the study.

Declaration of interests

WH and MG have received consultation fees from WHO. WH has received payment for expert testimony on the risks of cannabis use. MG is an appointed member of the Medicinal Cannabis Expert Working Group, Australian Department of Health, Ageing and Disability. MG has received funding from the Therapeutic Goods Administration for independent evidence reviews on medicinal cannabis. All other authors declare no competing interests.

Data sharing

Immediately following publication, proposals for the use and re-analysis of the data will be considered through liaising with the corresponding author.

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