

# Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis



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## Summary

**Background** Medicinal cannabinoids, including medicinal cannabis and pharmaceutical cannabinoids and their synthetic derivatives, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), have been suggested to have a therapeutic role in certain mental disorders. We analysed the available evidence to ascertain the effectiveness and safety of all types of medicinal cannabinoids in treating symptoms of various mental disorders.

**Methods** For this systematic review and meta-analysis we searched MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews for studies published between Jan 1, 1980, and April 30, 2018. We also searched for unpublished or ongoing studies on ClinicalTrials.gov, the EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry. We considered all studies examining any type and formulation of a medicinal cannabinoid in adults ( $\geq 18$  years) for treating depression, anxiety, attention-deficit hyperactivity disorder (ADHD), Tourette syndrome, post-traumatic stress disorder, or psychosis, either as the primary condition or secondary to other medical conditions. We placed no restrictions on language, publication status, or study type (ie, both experimental and observational study designs were included). Primary outcomes were remission from and changes in symptoms of these mental disorders. The safety of medicinal cannabinoids for these mental disorders was also examined. Evidence from randomised controlled trials was synthesised as odds ratios (ORs) for disorder remission, adverse events, and withdrawals and as standardised mean differences (SMDs) for change in symptoms, via random-effects meta-analyses. The quality of the evidence was assessed with the Cochrane risk of bias tool and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This study is registered with PROSPERO (CRD42017059372, CRD42017059373, CRD42017059376, CRD42017064996, and CRD42018102977).

**Findings** 83 eligible studies (40 randomised controlled trials,  $n=3067$ ) were included: 42 for depression (23 randomised controlled trials;  $n=2551$ ), 31 for anxiety (17 randomised controlled trials;  $n=605$ ), eight for Tourette syndrome (two randomised controlled trials;  $n=36$ ), three for ADHD (one randomised controlled trial;  $n=30$ ), 12 for post-traumatic stress disorder (one randomised controlled trial;  $n=10$ ), and 11 for psychosis (six randomised controlled trials;  $n=281$ ). Pharmaceutical THC (with or without CBD) improved anxiety symptoms among individuals with other medical conditions (primarily chronic non-cancer pain and multiple sclerosis; SMD  $-0.25$  [95% CI  $-0.49$  to  $-0.01$ ]; seven studies;  $n=252$ ), although the evidence GRADE was very low. Pharmaceutical THC (with or without CBD) worsened negative symptoms of psychosis in a single study (SMD  $0.36$  [95% CI  $0.10$  to  $0.62$ ];  $n=24$ ). Pharmaceutical THC (with or without CBD) did not significantly affect any other primary outcomes for the mental disorders examined but did increase the number of people who had adverse events (OR  $1.99$  [95% CI  $1.20$  to  $3.29$ ]; ten studies;  $n=1495$ ) and withdrawals due to adverse events ( $2.78$  [1.59 to 4.86]; 11 studies;  $n=1621$ ) compared with placebo across all mental disorders examined. Few randomised controlled trials examined the role of pharmaceutical CBD or medicinal cannabis.

**Interpretation** There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis. There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed.

**Funding** Therapeutic Goods Administration, Australia; Commonwealth Department of Health, Australia; Australian National Health and Medical Research Council; and US National Institutes of Health.

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*Lancet Psychiatry* 2019

Published Online

October 28, 2019

[https://doi.org/10.1016/S2215-0366\(19\)30401-8](https://doi.org/10.1016/S2215-0366(19)30401-8)

See Online/Comment

[https://doi.org/10.1016/S2215-0366\(19\)30375-X](https://doi.org/10.1016/S2215-0366(19)30375-X)

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### Research in context

#### Evidence before this study

We searched PubMed up to July 12, 2019, for reviews of cannabis use and mental health using the MeSH terms (((“medical marijuana”[MeSH Terms] OR (“medical”[All Fields] AND “marijuana”[All Fields]) OR “medical marijuana”[All Fields] OR (“medical”[All Fields] AND “cannabis”[All Fields]) OR “medical cannabis”[All Fields]) AND (“mental health”[MeSH Terms] OR (“mental”[All Fields] AND “health”[All Fields]) OR “mental health”[All Fields])) AND Review[ptyp]). This search led to 152 results, of which nine were relevant reviews (or summaries of reviews, as in the case of the US National Academies of Science) of cannabis or cannabinoids for mental health problems. The different reviews included varied study designs to examine the effects of cannabinoids on mental disorders; some concentrated on cross-sectional studies, others were limited to randomised controlled trials, and some were further limited to studies where the mental health symptoms were the primary indication for the cannabinoid. Some reviews pooled studies quantitatively on one outcome for a given mental disorder, but other features of their eligibility criteria and date of publication meant that few studies were included (eg, none for depression, one for anxiety, two for psychosis). All reviews concluded that the evidence was scarce but in many instances some concluded that no data yet existed for some mental health outcomes (eg, depression). No previous reviews defined a priori both primary and secondary outcomes of cannabinoids used for different mental disorders, nor did they systematically compile both randomised controlled trials and observational study designs. Most described potential adverse outcomes of cannabinoid use by relying on evidence from studies of people with recreational cannabis use or generally pooling adverse events from any study of medicinal cannabinoids, rather than specifically extracting and pooling data on adverse events and treatment withdrawals from the studies of cannabinoids in

people with mental disorders. The clarity with which the specific cannabinoids were documented varied across the reviews, as did the characteristics of the study populations and the studies that were extracted and reported.

#### Added value of this study

Our systematic review and meta-analysis represents, to our knowledge, the most up to date and detailed analysis of the available evidence for the effectiveness of cannabinoids for treating mental health symptoms and disorders. We prespecified primary and secondary outcomes to examine for each mental disorder, included studies where the condition was primary or secondary, systematically collated evidence from study designs other than randomised controlled trials, and pooled all outcomes and adverse event data quantitatively wherever possible. We also specified which cannabinoids were studied and where the data and gaps were across primary and secondary outcomes. We conclude that the available evidence for the effectiveness of cannabinoids in improving symptoms of anxiety is of very low quality. There is inadequate evidence to suggest that cannabinoids improve depressive disorders, symptoms of depression, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis.

#### Implications of all the available evidence

Our findings have direct policy relevance. In countries where cannabis and cannabinoids are being made available for medicinal use, and in which mental health problems are a common reason for requesting access to cannabinoids for medicinal purposes, these findings clarify where the evidence exists and the quality of such evidence. This study also highlights the need for investment into high-quality research efforts to study the effects of different cannabinoids on a range of outcomes for people with mental disorders.

### Introduction

Countries are increasingly allowing cannabinoids to be made available for medicinal purposes, including for the treatment of mental disorders. In our study, based on previous agreed terminology,<sup>1</sup> we use the term “medicinal cannabinoids” as an umbrella term encompassing all plant-derived and synthetic derivatives. We use “medicinal cannabis” to refer to any part of the cannabis plant and plant material, such as buds, leaves, or full plant extracts (eg, *Cannabis sativa*). We use the term “pharmaceutical cannabinoids” to refer to pharmaceutical-grade medicinal extracts with defined and standardised tetrahydrocannabinol (THC) with or without cannabidiol (CBD) content (eg, THC, CBD extract, or THC–CBD combinations such as nabiximols) and synthetic cannabinoid derivatives.<sup>1</sup> Given the increasing interest in CBD products for various medical conditions, we also separately grouped studies that only used pharmaceutical CBD.

After chronic non-cancer pain, mental health is one of the most common reasons for using medicinal cannabinoids.<sup>2</sup> In terms of biological plausibility, a potential role exists of the endocannabinoid system (CB1 receptors) in reducing depressive and stress symptoms<sup>3</sup> as well as the emotional and cognitive features of post-traumatic stress disorder.<sup>4</sup> CBD has been proposed as an effective short-term treatment for individuals with social anxiety disorder.<sup>5</sup> Medicinal cannabinoids have been reported to reduce tics in Tourette syndrome.<sup>6</sup> Many surveys report increased rates of cannabis use among people living with depression, anxiety, post-traumatic stress disorder, and psychosis, and self-medication of symptoms is suggested to be a driver of some of this use.<sup>7,8</sup>

Given the interest in the use of medicinal cannabinoids for these purposes, a thorough review of the available evidence is needed to inform policy and clinical decisions. Previous systematic reviews have been limited in their coverage of mental disorders, study designs, and use of

quantitative synthesis (ie, meta-analysis). A 2015 review by Whiting and colleagues,<sup>9</sup> which included five randomised controlled trials of mental disorders, found no effect of medicinal cannabinoids on psychosis or depression, but noted low-quality evidence for some improvement in Tourette syndrome and anxiety. A 2016 review by Wilkinson and colleagues<sup>10</sup> included 40 studies (randomised controlled trials and observational studies) of medicinal cannabinoids for post-traumatic stress disorder, Tourette syndrome, and Alzheimer's disease. No randomised controlled trials were identified for any condition and no meta-analysis was done, so no conclusions were made about efficacy. Crucially, highly prevalent disorders for which medicinal cannabinoids are often sought, such as depression, anxiety, and psychosis, were not included. The 2017 National Academy of Sciences (NAS) review<sup>11</sup> reported beneficial effects of medicinal cannabinoids for Tourette syndrome, anxiety, and post-traumatic stress disorder, and no effect on psychosis or depression; however, this review was based largely on findings reported by Whiting and colleagues.<sup>9</sup> No review has, to date, considered all types of evidence, the potential differential effects of different types of medicinal cannabinoids, and the safety of using cannabinoids for mental disorders. Disentangling the evidence for different types of cannabinoids for specific mental disorders is needed to direct research efforts and provide clinical guidance.<sup>1</sup>

We aimed to examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention-deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.

## Methods

### Search strategy and selection criteria

For this systematic review and meta-analysis, we searched MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Clinical Trials (CENTRAL), and the Cochrane Database of Systematic Reviews via Ovid for studies published from Jan 1, 1980, to Apr 30, 2018. Five separate searches were done to identify studies that investigated the efficacy of plant-based and pharmaceutical cannabinoids in reducing or treating symptoms of depression, anxiety, post-traumatic stress disorder, ADHD and Tourette syndrome, and psychotic disorders. The detailed search strategies for each condition are shown in the appendix (pp 5–9). To identify ongoing or

unpublished studies, we also searched ClinicalTrials.gov, the EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry using the keywords “cannabis”, “cannabinoids”, “marijuana”, and each of the six mental disorders. We also hand-searched reference lists of included studies and topical reviews for potentially relevant articles. No restrictions were placed on language, publication status, or publication type.

This study is registered on PROSPERO (depression: CRD42017059376; anxiety: CRD42017059373; post-traumatic stress disorder: CRD42017064996; ADHD and Tourette syndrome: CRD42017059372; psychosis: CRD42018102977).

We included studies examining the use of medicinal cannabinoids in adults aged 18 years or older for the purpose of treating depression, anxiety, ADHD and Tourette syndrome, post-traumatic stress disorder, and psychosis either as the primary condition or secondary to other medical conditions (such as chronic non-cancer pain). We chose to review these specific conditions because they are widely cited as reasons for using medicinal cannabinoids,<sup>2</sup> and have onset in young adulthood and thus have an impact across the lifespan.<sup>12</sup> We did not include neurocognitive disorders such as dementia as they have a markedly different pathophysiology and have onset later in life and thus warrant a separate, specific review.

We considered studies examining any type and formulation of medicinal cannabinoid: THC, CBD, combination THC plus CBD, *Cannabis sativa*, and other cannabinoids (eg, tetrahydrocannabinolic acid, cannabidiolic acid, cannabidivarin, and the synthetic  $\Delta^9$ -tetrahydrocannabinol formulations nabilone and dronabinol). We categorised these products into pharmaceutical grade THC (with or without CBD; labelled here as THC–CBD), pharmaceutical grade CBD, and medicinal cannabis.

As per existing reviews examining the efficacy of medicinal cannabinoids for chronic non-cancer pain<sup>13</sup> and epilepsy,<sup>14</sup> we included both experimental and observational study designs (ie, randomised controlled trials, non-randomised controlled trials, quasi-experimental studies, before-and-after studies, prospective and retrospective cohort studies, case-control studies, analytical cross-sectional studies, observational studies, self-reported studies, and N-of-1 studies). This approach allows researchers, clinicians, and policy makers to map current research activity and to identify knowledge gaps. For studies with a comparison group, we considered any type of comparator, including placebo, waitlist controls, and other interventions. We excluded reviews of mechanisms of cannabinoid systems, commentary articles, and clinical overviews that did not assess and synthesise individual studies.

To be eligible for inclusion, a study had to report on at least one primary outcome—either remission or change in mental disorder symptomatology. The full list of outcomes is provided in the panel.

See Online for appendix

**Panel: Primary and secondary outcomes considered for each of the disorders****Depression***Primary outcomes*

- Remission: absence of a depressive disorder diagnosis by use of validated scales
- Change in depressive symptoms by use of self-reported scales or items

*Secondary outcomes*

- Measures of global functioning, including quality of life, patient or caregiver global impression of change, and satisfaction with treatment

**Anxiety***Primary outcomes*

- Remission: absence of an anxiety disorder diagnosis by use of validated scales
- Change in anxiety symptoms by use of self-reported scales or items

*Secondary outcomes*

- Measures of global functioning, including quality of life, patient or caregiver global impression of change, and satisfaction with treatment

**Attention-deficit hyperactivity disorder (ADHD)***Primary outcomes*

- Change in ADHD symptom-related behaviour by use of standardised measures; any context
- Change in ADHD symptom-related behaviour in the home by use of standardised measures
- Change in ADHD symptom-related behaviour in school by use of standardised measures

*Secondary outcomes*

- Measures of global functioning, including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
- Change in cardiovascular effects
- Weight changes

**Tourette syndrome***Primary outcomes*

- Change in tic severity measured by use of standardised measures

*Secondary outcomes*

- Measures of global functioning, including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
- Change in cardiovascular effects
- Weight changes

**Post-traumatic stress disorder***Primary outcomes*

- Remission: absence of post-traumatic stress disorder diagnosis by use of validated and reliable clinician-rated scales
- Change in severity of self-reported traumatic stress symptoms by use of self-reported scales or items

*Secondary outcomes*

- Measures of global functioning, including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
- Change in severity of depressive symptoms by use of a standardised measure
- Change in severity of anxiety symptoms by use of a standardised measure
- Change in sleep quality
- Change in frequency of nightmares

**Psychosis***Primary outcomes*

- Whether patients still meet criteria for a diagnosis after treatment
- Change in positive and negative symptoms of psychosis

*Secondary outcomes*

- Measures of global functioning, including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
- Change in cognitive functioning
- Measures of emotional functioning, including depression, anxiety, mood, and social skills

**All six disorders***Secondary outcomes*

- 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

Two reviewers (DZ, GC, ES, or LTT) independently examined titles and abstracts by use of the web-based systematic review programme Covidence (Melbourne, Australia). Relevant articles were obtained in full and assessed for inclusion independently by the two reviewers. Disagreement between reviewers was resolved via discussion to reach consensus, and a third reviewer (LD, ES, NB, or GC) consulted if consensus could not be reached by the two initial reviewers.

### Data analysis

Data were extracted by two reviewers via a pre-piloted, standardised data extraction tool in Microsoft Excel 2016. We extracted data on details of the populations, interventions, comparisons, outcomes of significance to the mental disorder, study methods, cannabinoid dose and route of administration, placement in the therapeutic hierarchy, adverse events, and study withdrawals. When data were not reported in full, we contacted authors for additional information. When authors reported multiple analyses (eg, intention-to-treat, available case, or per-protocol), we extracted the more conservative analysis with a preference for intention-to-treat analyses. We reported adverse events according to high-level Medical Dictionary for Regulatory Activities (MedDRA) categories. We used Review Manager (RevMan), version 5.3, for all analyses, including calculations or transformation of available data to impute missing data (eg, confidence intervals, number of cases) in order to calculate required outcome data.

The panel outlines the primary and secondary outcomes for each condition. We planned to examine remission from the target mental disorder (where appropriate) and changes in symptoms of the target mental disorder as the primary outcomes. Secondary outcomes included changes in distal factors related to the mental disorder, including global functioning, cardiovascular effects, weight, and sleep (panel). All-cause, serious, and treatment-related adverse events, as well as all-cause study withdrawals and study withdrawals due to adverse events were examined as secondary outcomes for all disorders.

For randomised controlled trials, the risk of bias was assessed with the Cochrane risk of bias tool (further details of the tool used and the risk of bias plots are provided in the appendix pp 25–34),<sup>15</sup> which includes assessment of indicators of selection bias, performance bias, detection bias, attrition bias, and reporting bias. Risk of bias assessments were completed independently by two reviewers (LTT, DZ, or GC). Inter-reviewer disagreement was resolved via discussion to reach consensus, and a third reviewer (ES or GC) consulted if consensus could not be reached by the two initial reviewers.

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to rate the quality of the evidence for each

outcome.<sup>16</sup> This was done by one reviewer (NB) and checked by a second reviewer (LTT), and disagreements were resolved via discussion with two further reviewers (LD and GC). In this approach, evidence from randomised controlled trials is initially rated as “high quality” but can be downgraded up to three levels to “moderate quality”, “low quality”, or “very low quality” because of five categories of limitations. A high-quality rating indicates that we are confident that the true effect is similar to the estimated effect; a very-low-quality rating indicates that the true effect is likely to be substantially different from the estimated effect. Limitations considered are the risk of bias (ie, whether limitations in study design and execution would bias the effect estimate), indirectness of evidence (eg, whether the effects of cannabinoids on mental disorders had to be inferred from indirect evidence among those without the disorder), inconsistency of results (ie, high, unexplained heterogeneity), imprecision (ie, wide confidence intervals, including potentially covering appreciable benefit and harm), and publication bias (ie, selective publication of studies leading to a systematic bias in the effect estimate).

Meta-analyses included parallel and crossover randomised controlled trials. Continuous outcomes were pooled as standardised mean differences (SMDs) and dichotomous outcomes as odds ratios (ORs), with random-effects, generic inverse variance meta-analyses. A common rule of thumb for interpreting SMDs is as follows: 0.2 represents a small effect, 0.5 represents a medium effect, and 0.8 represents a large effect.<sup>17</sup> Heterogeneity was assessed with the  $I^2$  statistic.  $I^2$  values of 0–39% can be considered as unimportant, 40–74% as moderate or substantial, and 75–100% as high levels of inconsistency across studies.<sup>18</sup>

Analyses were stratified by mental disorder, the cannabinoid used (pharmaceutical THC–CBD, pharmaceutical CBD, or medicinal cannabis), and the comparator used (active or placebo). For each of these stratified analyses, we first pooled the evidence from all eligible randomised controlled trials, regardless of population studied. Where applicable (depression and anxiety studies only), we then did sensitivity analyses restricted to only those randomised controlled trials enrolling participants with the mental disorder. Where heterogeneity was substantial and sample sizes were sufficient, we did exploratory analyses to examine potential reasons for the heterogeneity. Finally, we pooled the evidence across randomised controlled trials (regardless of mental disorder) on the incidence of adverse events and withdrawals. Narrative synthesis of results from observational studies was done by summarising key results from each study, with the same stratification as for randomised controlled trials where possible. Further details of the approach taken for the meta-analysis, including methods used to manage variations in study design and avoid unit-of-analysis errors, are provided in the appendix (p 51).

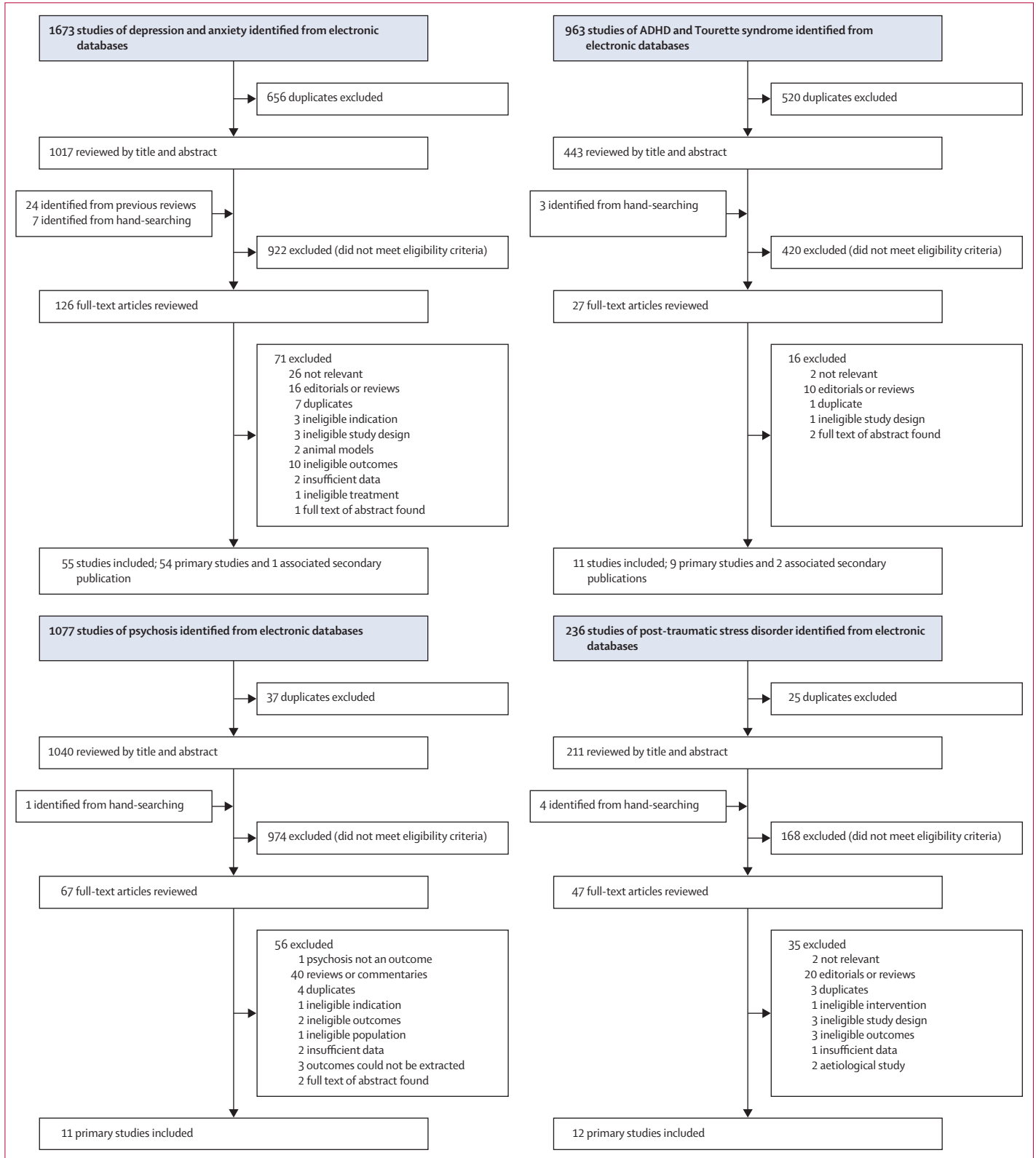


Figure: Study selection  
ADHD=attention-deficit hyperactivity disorder.



### Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

The PRISMA flowchart is shown in the figure, and the list of studies excluded at the full-text screening stage is provided in the appendix (pp 10–17). The appendix (pp 35–45) also shows the number of studies according to study designs of eligible studies for each mental health outcome and the characteristics of each included study. After screening, 83 eligible studies were identified (40 randomised controlled trials; n=3067): 42 for depression<sup>19–59</sup> (23 randomised controlled trials, including one unpublished study on EudraCT, 2012-003771-18; n=2551), 31 for anxiety<sup>5,19–22,24,25,27,29–31,36,37,39–41,43,45,47,50,55,60–69</sup> (17 randomised controlled trials; n=605), eight for Tourette syndrome<sup>6,40,62,66,70–73</sup> (two randomised controlled trials; n=36), three for ADHD<sup>6,71,74</sup> (one randomised controlled trial; n=30), 12 for post-traumatic stress disorder<sup>34,67,68,75–83</sup> (one randomised controlled trial; n=10), and 11 for psychosis<sup>84–94</sup> (six randomised controlled trials; n=281). The appendix (pp 18–25) lists ongoing and incomplete trials identified in the clinical trials registries.

Table 1 summarises the characteristics of included randomised controlled trials. Medicinal cannabinoids were mostly investigated as adjuvant medicines. Randomised controlled trials were typically very small (with median sample sizes of 10–39 participants across mental disorders), with short follow-up periods (median trial length 4–5 weeks). Across disorders, most randomised controlled trials examined pharmaceutical THC; most commonly, these were nabiximols and nabilone. The exception was randomised controlled trials of psychosis, which primarily examined pharmaceutical CBD. Few randomised controlled trials examined medicinal cannabis as the treatment.

In most randomised controlled trials examining depression and anxiety, the primary indication for the cannabinoid was another medical condition, with chronic non-cancer pain followed by multiple sclerosis being the most common primary conditions. In studies of other mental disorders, the mental health outcome was the primary indication for the cannabinoid.

A summary of the risk of bias of included studies is provided in the appendix (pp 25–34). Briefly, most randomised controlled trials reported adequate randomisation sequence generation and concealment; however, the majority were of unclear or high risk of bias for masking of participants, personnel, and outcome assessors. Most studies had other potential, albeit unclear, sources of bias, such as use of post-hoc analyses and unclear adjustment for crossover trials.

	Depression (n=23)	Anxiety (n=17)	ADHD (n=1)	Tourette syndrome (n=2)	Post-traumatic stress disorder (n=1)	Psychosis (n=6)
<b>Region</b>						
North America	8	6	0	0	1	3
Western Europe	12	10	1	2	0	1
Other and multiple regions	3	1	0	0	0	2
<b>Year of study</b>						
1980–1990	0	1	0	0	0	0
1991–2000	0	0	0	0	0	0
2001–2010	13	9	0	2	0	2
2011 onwards	10	7	1	0	1	4
<b>Conflict of interest declared?</b>						
Yes; none	9	6	0	0	1	2
Yes; potential conflict	9	5	0	1	0	3
Not declared	5	6	1	1	0	1
<b>Participant characteristics</b>						
Total number of participants	2551	605	30	36	10	281
Median number of participants	34 (26–84)	30 (20–40)	30 (NA)	18 (15–21)	10 (NA)	39 (35–50)
Median age, years	49.8 (47.6–52.2)	47.6 (34.0–49.8)	NR	33.5 (33.3–33.8)	44 (NA)	34.7 (30.1–40.8)
<b>Primary health condition of study participants</b>						
Depression	0	0	0	0	0	0
Anxiety disorder	0	3	0	0	0	0
Tourette syndrome	1	2	0	2	0	0
ADHD	0	0	1	0	0	0
Post-traumatic stress disorder	0	0	0	0	1	0
Psychotic disorder	0	0	0	0	0	6
Multiple sclerosis	7	2	0	0	0	0
Chronic non-cancer pain	10	7	0	0	0	0
Parkinson's disease	0	0	0	0	0	0
Other	5	3	0	0	0	0
<b>Primary indication</b>						
Depression	2	1	0	0	0	0
Anxiety	1	4	0	0	0	2
Analgesia	14	9	0	0	0	0
Tic severity	1	2	0	2	0	0
Sleep	2	2	0	0	0	1
ADHD symptoms	0	0	1	0	0	0
Post-traumatic stress disorder symptoms	0	0	0	0	1	0
Spasticity	5	1	0	0	0	0
Psychosis	0	0	0	0	0	4
Proportion of cannabinoid-naïve	38.5%	71.0%	33.3%	56.3%	NR	17.2%
Number of studies with cannabinoid-naïve participants	10	7	1	2	1	2

(Table 1 continues on next page)

	Depression (n=23)	Anxiety (n=17)	ADHD (n=1)	Tourette syndrome (n=2)	Post-traumatic stress disorder (n=1)	Psychosis (n=6)
(Continued from previous page)						
Cannabinoid used						
Cannabis sativa	5	1	0	0	0	0
THC extract	2	3	0	2	0	1
Nabiximols	7	3	1	0	0	0
THC-CBD extract	1	1	0	0	0	0
CBD	0	2	0	0	0	5
Dronabinol	5	2	0	0	0	0
Nabilone	3	5	0	0	1	0
THC-HS	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Pharmaceutical grade						
Yes	18	15	1	2	2	5
No	4	1	0	0	0	0
Unsure or unknown	1	1	0	0	0	1
Route of administration						
Vaporised	2	0	0	0	0	0
Smoked	3	1	0	0	0	0
Oral	10	12	0	2	1	3
Oral mucosal spray	8	4	1	0	0	0
Mixed routes	0	0	0	0	0	0
Not recorded or unclear	0	0	0	0	0	2
Intravenous	0	0	0	0	0	1
Rectal	0	0	0	0	0	0
Median treatment, weeks	5 (3-12)	4 (1-8)	6 (NA)	3 (2-5)	7 (NA)	4 (1-6)
Place in therapeutic hierarchy						
Primary	0	3	1	0	0	1
Adjuvant	20	12	0	2	1	5
Not reported, unclear	3	2	0	0	0	0

Data are n or median (IQR), unless otherwise indicated. NA=not available. ADHD=attention-deficit hyperactivity disorder. NR=not reported. THC=Δ<sup>9</sup> tetrahydrocannabinol. HS=hemisuccinate. CBD=cannabidiol.

**Table 1: Summary of randomised controlled trials of medicinal cannabinoids for treatment of mental health symptoms and disorders**

Results of all meta-analyses of randomised controlled trials of cannabinoids for the treatment of mental health symptoms and disorders are described below and reported in full in table 2 for pharmaceutical THC-CBD, in table 3 for pharmaceutical CBD, and in the appendix (p 53) for medicinal cannabis. Adverse events and withdrawals for pharmaceutical THC-CBD, pharmaceutical CBD, and medicinal cannabis are described below and reported in full in table 4. Forest plots for primary outcomes are displayed in the appendix (pp 46–50).

Pharmaceutical THC-CBD did not significantly improve symptoms of depression compared with either active comparators<sup>45</sup> or placebo<sup>20,23,36,39,40,46,47,50,52,56,58</sup> in randomised trials, including one unpublished study on EudraCT, 2012-003771-18 (table 2). The evidence GRADE was very low, partly because of indirectness since none of the included randomised controlled trials comprised participants with a primary diagnosis of depression;

most included participants with multiple sclerosis. Following the suggestion of a reviewer, we did an exploratory analysis to examine whether length of follow-up contributed to the substantial heterogeneity seen ( $I^2=67%$ ). One study<sup>40</sup> administered pharmaceutical THC-CBD and assessed participants on a single day, whereas the remaining studies used longer treatment and follow-up periods (range 2–15 weeks). Removing the single shorter study made minimal difference to the effect size and heterogeneity (SMD  $-0.05$  [95% CI  $-0.22$  to  $0.13$ ]; 11 studies,  $n=1632$ ;  $I^2=70%$ ).

No randomised controlled trials examining CBD for depression outcomes were identified. A single, small randomised controlled trial examining medicinal cannabis for depression outcomes among participants with chronic non-cancer pain found no change in depressive symptoms compared with placebo (appendix p 53).<sup>54</sup>

Pharmaceutical THC-CBD led to significantly greater reductions in anxiety symptoms than did placebo (SMD  $-0.25$  [95% CI  $-0.49$  to  $-0.01$ ]; seven studies,  $n=252$ ;  $I^2=65%$ ),<sup>20,36,39,40,47,50,69</sup> with no difference seen in the single, small study that used an active comparator (table 2).<sup>45</sup> The evidence GRADE was very low, in part because none of the studies included participants with a primary diagnosis of anxiety; most included participants with chronic non-cancer pain or multiple sclerosis. Reporting bias also contributed to the very low GRADE rating; outcomes of three randomised controlled trials could not be included in this synthesis because of incomplete data reporting.<sup>41,61,63</sup> One study showed a beneficial effect of pharmaceutical THC-CBD over placebo, whereas the other two showed no significant difference. Given that the confidence intervals of the effect are close to zero, had it been possible to include these studies it is likely that the benefit of pharmaceutical THC-CBD over placebo would no longer be significant.

We did an exploratory analysis to ascertain whether varying lengths of follow-up contributed to the substantial heterogeneity seen in the pharmaceutical THC-CBD versus placebo comparison ( $I^2=65%$ ). One study<sup>40</sup> administered pharmaceutical THC-CBD and assessed participants on a single day, whereas the remaining studies used longer treatment and follow-up periods (range 3–12 weeks). Removing the single shorter study reduced the heterogeneity to an unimportant level and the beneficial effect of pharmaceutical THC-CBD remained significant (SMD  $-0.34$  [95% CI  $-0.53$  to  $-0.14$ ]; six studies,  $n=228$ ;  $I^2=36%$ ).

Two studies examined the effect of CBD—both in participants with social anxiety—and did not find a significant improvement in anxiety symptoms compared with placebo (table 3).<sup>5,60</sup> No randomised controlled trials examined the impact of medicinal cannabis on anxiety outcomes (appendix p 53).

The single, small randomised controlled trial identified for ADHD compared pharmaceutical THC-CBD with placebo among participants with ADHD.<sup>74</sup> No significant



	Comparator	Studies (participants)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled SMD (95% CI)	I <sup>2</sup>	Favours	GRADE
<b>Depression</b>											
Primary outcomes											
Remission from disorder	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in depressive symptoms*	Active	1 (52)	Not serious	Very serious	Serious	Serious	Undetected	0.00 (-0.17 to 0.17)	NA	Neither	Very low
Change in depressive symptoms*	Placebo	12 (1656)	Not serious	Very serious	Serious	Not serious	Likely	-0.05 (-0.20 to 0.11)	67%	Neither	Very low
Secondary outcomes											
Change in global functioning	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>Anxiety</b>											
Primary outcomes											
Remission from disorder	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in anxiety symptoms*	Active	1 (52)	Not serious	Very serious	Serious	Serious	Undetected	-0.12 (-0.30 to 0.05)	NA	Neither	Very low
Change in anxiety symptoms*	Placebo	7 (252)	Serious	Serious	Serious	Serious	Likely	-0.25 (-0.49 to -0.01)	65%	THC-CBD	Very low
Secondary outcomes											
Change in global functioning	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>ADHD</b>											
Primary outcomes											
Change in ADHD symptoms, any location*	Placebo	1 (30)	Not serious	Not serious	Serious	Serious	Undetected	-0.67 (-1.41 to 0.07)	NA	Neither	Low
Change in ADHD symptoms, home	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in ADHD symptoms, school	..	0 (0)	..	..	..	..	..	..	..	..	..
Secondary outcomes											
Change in global functioning	Placebo	1 (30)	Not serious	Not serious	Serious	Serious	Undetected	0.00 (-0.72 to 0.72)	NA	Neither	Low
Cardiovascular effects	..	0 (0)	..	..	..	..	..	..	..	..	..
Weight change	Placebo	1 (30)	Not serious	Not serious	Serious	Serious	Undetected	0.14 (-0.58 to 0.85)	NA	Neither	Low
<b>Tourette syndrome</b>											
Primary outcomes											
Change in tic or Tourette symptoms*	Placebo	2 (41)	Not serious	Not serious	Serious	Serious	Undetected	-0.46 (-1.32 to 0.40)	68%	Neither	Low
Secondary outcomes											
Change in global functioning	Placebo	2 (41)	Not serious	Not serious	Serious	Very serious	Undetected	-0.84 (-2.10 to 0.42)	68%	Neither	Very low
Cardiovascular effects	..	0 (0)	..	..	..	..	..	..	..	..	..
Weight change	..	0 (0)	..	..	..	..	..	..	..	..	..

(Table 2 continues on next page)

effect was seen on the primary outcome of ADHD symptoms (table 2). With regard to the secondary outcomes, the study also showed no significant effect of pharmaceutical THC-CBD versus placebo on global functioning or weight change. No studies examined the impact of CBD or medicinal cannabis on ADHD outcomes (appendix p 53).

The two small randomised controlled trials identified for Tourette syndrome compared pharmaceutical THC-CBD with placebo among participants with Tourette syndrome.<sup>40,66</sup> The pooled effect from these two,

small studies showed no significant benefit of pharmaceutical THC-CBD compared to placebo on Tourette symptoms (table 2). Similarly, no significant effect was seen for the secondary outcome of global functioning. No studies examined the impact of CBD or medicinal cannabis on outcomes of Tourette syndrome (appendix p 53).

We identified a single, small, randomised controlled trial of participants with post-traumatic stress disorder; this study did not report either of our primary outcomes.<sup>78</sup> Of the secondary outcomes, this study found a significant

	Comparator	Studies (participants)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled SMD (95% CI)	I <sup>2</sup>	Favours	GRADE
(Continued from previous page)											
<b>Post-traumatic stress disorder</b>											
Primary outcomes											
Remission from disorder	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in symptoms	..	0 (0)	..	..	..	..	..	..	..	..	..
Secondary outcomes											
Change in global functioning	Placebo	1 (19)	Not serious	Not serious	Serious	Serious	Undetected	-1.13 (-1.48 to -0.77)	NA	THC-CBD	Low
Change in depressive symptoms	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in anxiety symptoms	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in sleep quality	Placebo	1 (19)	Not serious	Not serious	Serious	Serious	Undetected	-0.10 (-0.38 to 0.18)	NA	Neither	Low
Change in nightmare frequency	Placebo	1 (19)	Not serious	Not serious	Serious	Serious	Undetected	-1.11 (-1.46 to -0.76)	NA	THC-CBD	Low
<b>Psychosis</b>											
Primary outcomes											
Remission from disorder	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in total symptoms	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in positive symptoms*	Placebo	1 (24)	Not serious	Not serious	Serious	Serious	Undetected	-0.20 (-0.45 to 0.06)	NA	Neither	Low
Change in negative symptoms*	Placebo	1 (24)	Not serious	Not serious	Serious	Serious	Undetected	0.36 (0.10 to 0.62)	NA	Placebo	Low
Secondary outcomes											
Change in global functioning	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in cognitive function	Placebo	1 (24)	Not serious	Not serious	Serious	Serious	Undetected	1.08 (0.71 to 1.45)	NA	Placebo	Low
Change in emotional functioning	..	0 (0)	..	..	..	..	..	..	..	..	..

SMD=standardised mean difference. GRADE=Grading of Recommendations, Assessment, Development and Evaluation. NA=not applicable. ADHD=attention-deficit hyperactivity disorder. THC=Δ<sup>9</sup> tetrahydrocannabinol. CBD=cannabidiol. \*Outcomes for which forest plots are available in the appendix (pp 46–50). In all comparisons the control group (placebo or active) is the reference group.

**Table 2: Summary of evidence from randomised controlled trials on the use of pharmaceutical THC-CBD (THC alone or THC-CBD preparations) for the treatment of mental health symptoms and disorders**

benefit of pharmaceutical THC-CBD compared with placebo in improving global functioning and nightmare frequency, and no significant effect on sleep quality (table 2). No studies examined the impact of CBD or medicinal cannabis on post-traumatic stress disorder outcomes (appendix p 53).

A single, small randomised controlled trial reported on the use of pharmaceutical THC-CBD among participants with psychosis.<sup>86</sup> This study found no significant change in positive symptoms (table 2) but a worsening of negative symptoms of psychosis (SMD 0.36 [95% CI 0.10 to 0.62]; n=24) with THC-CBD compared with placebo. Of the secondary outcomes, this study also found that pharmaceutical THC-CBD worsened cognitive functioning (SMD 1.08 [95% CI 0.71 to 1.45]; n=24).

The remaining randomised controlled trials of psychosis examined CBD. Across the one or two studies that reported on primary outcomes, CBD did not significantly improve total symptoms, positive symptoms, or negative symptoms,

compared with placebo<sup>85,92</sup> or active<sup>90</sup> comparators (table 3). With regard to the secondary outcomes, CBD led to an improvement in global functioning compared with placebo in the single study reporting this outcome (SMD -0.62 [95% CI -1.14 to -0.09]; n=86),<sup>92</sup> but did not significantly improve cognitive or emotional functioning.<sup>85,88,90,92</sup>

We identified no studies examining the impact of medicinal cannabis on psychosis outcomes (appendix p 53).

We pooled adverse events and study withdrawals from all randomised controlled trials (table 4). Pharmaceutical THC-CBD led to significantly more adverse events (OR 1.99 [95% CI 1.20 to 3.29]; ten studies, n=1495; I<sup>2</sup>=59%) and withdrawals due to adverse events (2.78 [1.59 to 4.86]; 11 studies, n=1621; I<sup>2</sup>=22%) than did placebo treatment. The evidence GRADE was low to moderate, because of inconsistency and indirectness (ie, participants in most of the analysed studies did not have a mental disorder). We estimated that one additional participant would

	Comparator	Studies (participants)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled SMD (95% CI)	I <sup>2</sup>	Favours	GRADE
<b>Depression</b>											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>Anxiety</b>											
Primary outcomes											
Remission from disorder	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in anxiety symptoms*	Placebo	2 (44)	Not serious	Not serious	Serious	Very serious	Undetected	-0.87 (-2.01 to 0.27)	85%	Neither	Very low
Secondary outcomes											
Change in global functioning	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>ADHD</b>											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>Tourette syndrome</b>											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>Post-traumatic stress disorder</b>											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>Psychosis</b>											
Primary outcomes											
Remission from disorder	..	0 (0)	..	..	..	..	..	..	..	..	..
Change in total symptoms*	Active	1 (39)	Not serious	Not serious	Serious	Serious	Undetected	-0.02 (-0.65 to 0.60)	NA	Neither	Low
Change in total symptoms*	Placebo	2 (122)	Not serious	Not serious	Serious	Serious	Undetected	0.05 (-0.50 to 0.61)	52%	Neither	Low
Change in positive symptoms*	Active	1 (39)	Not serious	Not serious	Serious	Serious	Undetected	-0.10 (-0.73 to 0.53)	NA	Neither	Low
Change in positive symptoms*	Placebo	2 (122)	Not serious	Not serious	Serious	Serious	Undetected	-0.17 (-0.69 to 0.35)	47%	Neither	Low
Change in negative symptoms*	Active	1 (39)	Not serious	Not serious	Serious	Serious	Undetected	-0.48 (-1.12 to 0.16)	NA	Neither	Low
Change in negative symptoms*	Placebo	2 (122)	Not serious	Not serious	Not serious	Serious	Undetected	0.08 (-0.27 to 0.44)	0%	Neither	Moderate
Secondary outcomes											
Change in global functioning	Placebo	1 (86)	Not serious	Not serious	Serious	Serious	Undetected	-0.62 (-1.14 to -0.09)	NA	CBD	Low
Change in cognitive function	Placebo	3 (150)	Not serious	Not serious	Not serious	Serious	Undetected	-0.01 (-0.33 to 0.32)	0%	Neither	Moderate
Change in emotional functioning	Active	1 (39)	Not serious	Not serious	Serious	Serious	Undetected	0.27 (-0.36 to 0.90)	NA	Neither	Low
Change in emotional functioning	Placebo	2 (122)	Not serious	Not serious	Serious	Serious	Likely	0.10 (-0.49 to 0.69)	57%	Neither	Very low

In all comparisons the control group (placebo or active) is the reference group. SMD=standardised mean difference. GRADE=Grading of Recommendations, Assessment, Development and Evaluation. ADHD=attention-deficit hyperactivity disorder. NA=not applicable. \*Outcomes for which forest plots are available in the appendix (pp 46–50).

**Table 3: Summary of evidence from randomised controlled trials on the use of pharmaceutical cannabidiol for the treatment of mental health symptoms and disorders**

experience an adverse event for every seven (95% CI 5–25) participants treated with pharmaceutical THC–CBD (number needed to treat to harm). Furthermore, one additional participant would withdraw because of an adverse event for every 14 (95% CI 7–39) participants treated with pharmaceutical THC–CBD. No significant differences between pharmaceutical THC–CBD and comparators were seen with regard to serious adverse events, treatment-related adverse events, or all-cause withdrawals.

Few randomised controlled trials examined adverse events and withdrawals due to CBD or medicinal cannabis,

and these studies found no significant increases in the number of people having adverse events or withdrawing compared with active and placebo comparators (table 4).

The findings of all included observational studies are detailed in the appendix (pp 35–45). Here, we summarise the findings of studies in which mental health was the primary indication in open-label or prospective cohorts. We identified no open-label or prospective cohort studies in which depression was the primary outcome; in ten observational studies depression was a secondary outcome in patients with chronic non-cancer pain or multiple sclerosis (seven open-label and three prospective

	Comparator	Studies (participants)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled OR (95% CI)	I <sup>2</sup>	Group with more adverse events or withdrawals	GRADE
<b>THC-CBD</b>											
<b>Adverse events</b>											
Adverse events, all-cause*	Active	1 (60)	Not serious	Serious	Serious	Very serious	Undetected	1.59 (0.57 to 4.45)	NA	Neither	Very low
Adverse events, all-cause*	Placebo	10 (1495)	Not serious	Serious	Serious	Not serious	Undetected	1.99 (1.20 to 3.29)	59%	THC-CBD	Low
Serious adverse events, all-cause	Placebo	4 (954)	Not serious	Serious	Not serious	Serious	Undetected	1.29 (0.94 to 1.77)	0%	Neither	Low
Treatment-emergent adverse events, all-cause	Placebo	2 (385)	Not serious	Serious	Not serious	Serious	Undetected	1.32 (0.79 to 2.20)	0%	Neither	Low
<b>Withdrawals</b>											
Withdrawals, all-cause	Placebo	15 (2299)	Not serious	Serious	Not serious	Serious	Likely	1.51 (0.96 to 2.36)	42%	Neither	Very low
Withdrawals due to adverse events*	Active	2 (252)	Not serious	Serious	Not serious	Serious	Undetected	0.54 (0.17 to 1.68)	0%	Neither	Low
Withdrawals due to adverse events*	Placebo	11 (1621)	Not serious	Serious	Not serious	Not serious	Undetected	2.78 (1.59 to 4.86)	22%	THC-CBD	Moderate
<b>CBD</b>											
<b>Adverse events</b>											
Adverse events, all-cause*	Placebo	1 (88)	Not serious	Not serious	Serious	Serious	Undetected	0.97 (0.40 to 2.33)	NA	Neither	Low
Serious adverse events, all-cause	Placebo	1 (88)	Not serious	Not serious	Serious	Very serious	Undetected	0.34 (0.01 to 8.60)	NA	Neither	Very low
Treatment-emergent adverse events, all-cause	Placebo	1 (88)	Not serious	Not serious	Serious	Serious	Undetected	1.06 (0.39 to 2.87)	NA	Neither	Low
<b>Withdrawals</b>											
Withdrawals, all-cause	Active	1 (42)	Not serious	Not serious	Serious	Very serious	Undetected	3.33 (0.32 to 34.99)	NA	Neither	Very low
Withdrawals, all-cause	Placebo	1 (88)	Not serious	Not serious	Serious	Very serious	Undetected	1.61 (0.26 to 10.16)	NA	Neither	Very low
Withdrawals due to adverse events*	Placebo	1 (88)	Not serious	Not serious	Serious	Very serious	Undetected	1.05 (0.06 to 17.30)	NA	Neither	Very low
<b>Cannabis</b>											
<b>Adverse events</b>											
Adverse events, all-cause	..	0 (0)	..	..	..	..	..	..	..	..	..
Serious adverse events, all-cause	..	0 (0)	..	..	..	..	..	..	..	..	..
Treatment-emergent adverse events, all-cause	..	0 (0)	..	..	..	..	..	..	..	..	..
<b>Withdrawals</b>											
Withdrawals, all-cause	Placebo	3 (209)	Serious	Serious	Not serious	Very serious	Undetected	1.41 (0.51 to 3.88)	7%	Neither	Very low
Withdrawals due to adverse events	..	0 (0)	..	..	..	..	..	..	..	..	..

In all comparisons the control group (placebo or active) is the reference group. THC-CBD includes pharmaceutical THC alone and pharmaceutical THC plus CBD combinations. OR=odds ratio. GRADE=Grading of Recommendations, Assessment, Development and Evaluation. THC=Δ<sup>9</sup> tetrahydrocannabinol. NA=not applicable. CBD=pharmaceutical cannabidiol. \*Outcomes for which forest plots are available in the appendix (pp 46-50).

**Table 4: Summary of evidence from randomised controlled trials on the safety of medicinal cannabinoids**

cohort studies). Eight open-label and prospective cohort studies reported on anxiety outcomes. Anxiety was a primary outcome in only one study of five participants,<sup>63</sup> which found that nabilone significantly reduced anxiety. We found no open-label or observational studies for ADHD or Tourette syndrome. Two open-label and two prospective cohort studies were identified in which post-traumatic stress disorder was the primary outcome; three studies involved cannabis and one involved THC extract. Three studies found reductions in post-traumatic stress disorder symptoms,<sup>79,81,82</sup> whereas one found that symptoms worsened with cannabis use in people with post-traumatic stress disorder and comorbid mental disorder.<sup>83</sup> We identified one open-label study where psychosis was the primary outcome, which found that CBD reduced psychosis symptoms.<sup>93</sup>

## Discussion

To our knowledge, this is the most comprehensive systematic review and meta-analysis examining the available evidence for medicinal cannabinoids in treating mental disorders and symptoms. There is a notable absence of high-quality evidence where mental disorders are the primary target of treatment, and most evidence is derived from studies where mental disorders are secondary to another medical condition, commonly chronic non-cancer pain and multiple sclerosis. Most of the included studies were done among individuals in whom depression or anxiety was secondary to another medical condition, and in these studies we found no impact of pharmaceutical THC (with or without CBD) on depression symptoms, and a small reduction in anxiety symptoms. Of the few studies in which participants had an anxiety disorder, we did not see a significant benefit of CBD on symptoms of anxiety. Single studies found that pharmaceutical THC–CBD improved global functioning in post-traumatic stress disorder and pharmaceutical CBD improved global functioning in psychosis. Across the small numbers of included studies, we did not find evidence that any type of cannabinoid significantly improves primary outcomes of ADHD, Tourette syndrome, post-traumatic stress disorder, or psychosis. In fact, results from one study suggested that pharmaceutical THC–CBD worsened negative symptoms of psychosis.

Cannabinoids are often advocated as a treatment for various mental disorders. Countries that allow medicinal cannabinoid use will probably see increased demand for such use. Clinicians and consumers need to be aware of the low quality and quantity of evidence for the effectiveness of medicinal cannabinoids in treating mental disorders and the potential risk of adverse events. Most studies are based on pharmaceutical cannabinoids, rather than medicinal cannabis (see appendix p 53), but plant products are most often used by those taking cannabinoids for medicinal purposes in the USA.<sup>8</sup> Although 16 trials are underway to examine the effectiveness of pharmaceutical CBD for specific conditions, including seven in psychosis,

few or no clinical studies to date have examined the effectiveness of CBD for depression, anxiety, Tourette syndrome, or ADHD (appendix pp 18–24).

The risk of adverse outcomes among individuals using medicinal cannabis products is indicated by a large body of research on the adverse effects of non-medical cannabis use. This research suggests that cannabis use can increase the occurrence of depression, anxiety, and psychotic symptoms.<sup>11,95–99</sup> The evidence of the risks of cannabis is not derived solely from observational studies of people using cannabis non-medically. For example, experimental evidence from a double-blind, randomised, placebo-controlled and crossover trial indicates the acute effects of smoked cannabis (containing 13% THC) on psychosis symptoms; this study found that cannabis increased the risk of acute psychotic symptoms.<sup>99</sup> Additionally, young adults (the age group at greatest risk of depression, anxiety, and psychosis) who use cannabis daily over extended periods are at risk of developing dependence.<sup>95</sup> These risks, and the limitations of existing evidence, need to be weighed when considering the use of medicinal cannabinoids to treat symptoms of common mental disorders. Those who decide to proceed should be carefully monitored for positive and negative mental health effects of using medicinal cannabinoids.

The strengths of our study included our comprehensive search strategy (including clinical trials registries), consideration of the full range and potential distinct effects of different types of cannabinoids, and the range of outcomes considered. Compared to previous reviews, we identified more studies (eg, for psychosis we identified six randomised controlled trials *vs* two in a previous review<sup>9</sup>). Nonetheless, our analyses and conclusions are limited by the small amount of available data, small study sizes, and heterogeneity of findings across studies. Small study sizes are of particular concern as effects have been identified to be larger in small studies of medicinal cannabinoids for chronic non-cancer pain.<sup>13</sup> Moreover, various independent analyses were done and hence might not retain significance if they are adjusted for multiple comparisons. However, no recommended approach exists for addressing multiplicity in systematic reviews, and we attempted to minimise this by choosing few primary outcomes, keeping subgroups to a minimum, and testing effects at a single time-point only.<sup>100,101</sup> Few randomised controlled trials, typically of very small size, have been done to date, so the absence of significant effects for ADHD and Tourette syndrome could well reflect the sparse evidence base. Studies of medicinal cannabinoids primarily for people diagnosed with depression and anxiety are needed. The reductions in anxiety symptoms identified in this systematic review and meta-analysis might have been due to improvements in the primary medical condition (chronic non-cancer pain or multiple sclerosis). Future research should therefore focus on the



effectiveness of cannabinoids in patients diagnosed with primary depression and anxiety.

The use of pharmaceutical cannabinoids and medicinal cannabis to treat symptoms of mental disorders is increasing. Our study is the most comprehensive review of the evidence to date, including both randomised controlled trials and observational studies of depression, anxiety, ADHD, Tourette syndrome, post-traumatic stress disorder, and psychosis. We found little evidence for the effectiveness of pharmaceutical CBD or medicinal cannabis for the treatment of any of these mental disorders. Some very-low-quality evidence was found for the use of pharmaceutical THC (with or without CBD) in treating anxiety symptoms among individuals with other medical conditions, such as chronic non-cancer pain and multiple sclerosis. We need high-quality randomised controlled trials to properly assess the effectiveness and safety of medicinal cannabinoids, compared with placebo and standard treatments, for the treatment of mental disorders. This evidence is essential before clinical guidelines can be provided about the medicinal use of cannabinoids for these disorders. In light of the paucity of evidence and absence of good quality evidence, and the known risk of cannabinoids, the use of cannabinoids as treatments for mental disorders cannot be justified at this time.

#### Contributors

LD and MF conceived the study. ES, GC, LTT, and DZ did the systematic search, selected papers, and extracted data. NB did the statistical analyses. LD, NB, GC, LTT, ES, and WDH drafted the manuscript with critical revisions from all authors. All authors reviewed the paper before submission.

#### Declaration of interests

MF and LD have been investigators on untied (ie, no control of the company over the conduct, reporting, or publication of study findings) investigator-driven educational grants funded by Reckitt Benckiser, Mundipharma, and Seqirus. MF, GC, and LD have been investigators on untied investigator-driven educational grants funded by Indivior. All other authors declare no competing interests.

#### Acknowledgments

We thank Mary Kumvaj who assisted in the development of the search strategy; and Harriet Townsend, Alana Garton, Rakin Rahman, and Megan Weier, who assisted with searches and screening. Funding was received from the Health Products Regulation Group, Commonwealth Department of Health. ES, GC, and LD are supported by NHMRC research fellowships (grant numbers 1104600, 1119992, and 1135991). LD is also supported by NIH grant NIDA R01DA1104470. The National Drug and Alcohol Research Centre is supported by funding from the Australian Government's Department of Health under the Drug and Alcohol Programme.

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