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 We also searched for unpublished or ongoing studies on ClinicalTrials.gov, the EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry.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 (≥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.

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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,[1] 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.[1] 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.[2] In terms of biological plausibility, a potential role exists of the endocannabinoid system (CB1 receptors) in reducing depressive and stress symptoms[3] as well as the emotional and cognitive features of post-traumatic stress disorder.[4] CBD has been proposed as an effective short-term treatment for individuals with social anxiety disorder.[5] Medicinal cannabinoids have been reported to reduce tics in Tourette syndrome.[6] 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.[7,8]

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,[9] 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[10] 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[11] 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.[9] 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.[1]

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,[2] and have onset in young adulthood and thus have an impact across the lifespan.[12] 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 Δ9-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[13] and epilepsy,[14] 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 symptomology. 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),[15] 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.[16] 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.[17] 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.[18]

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).

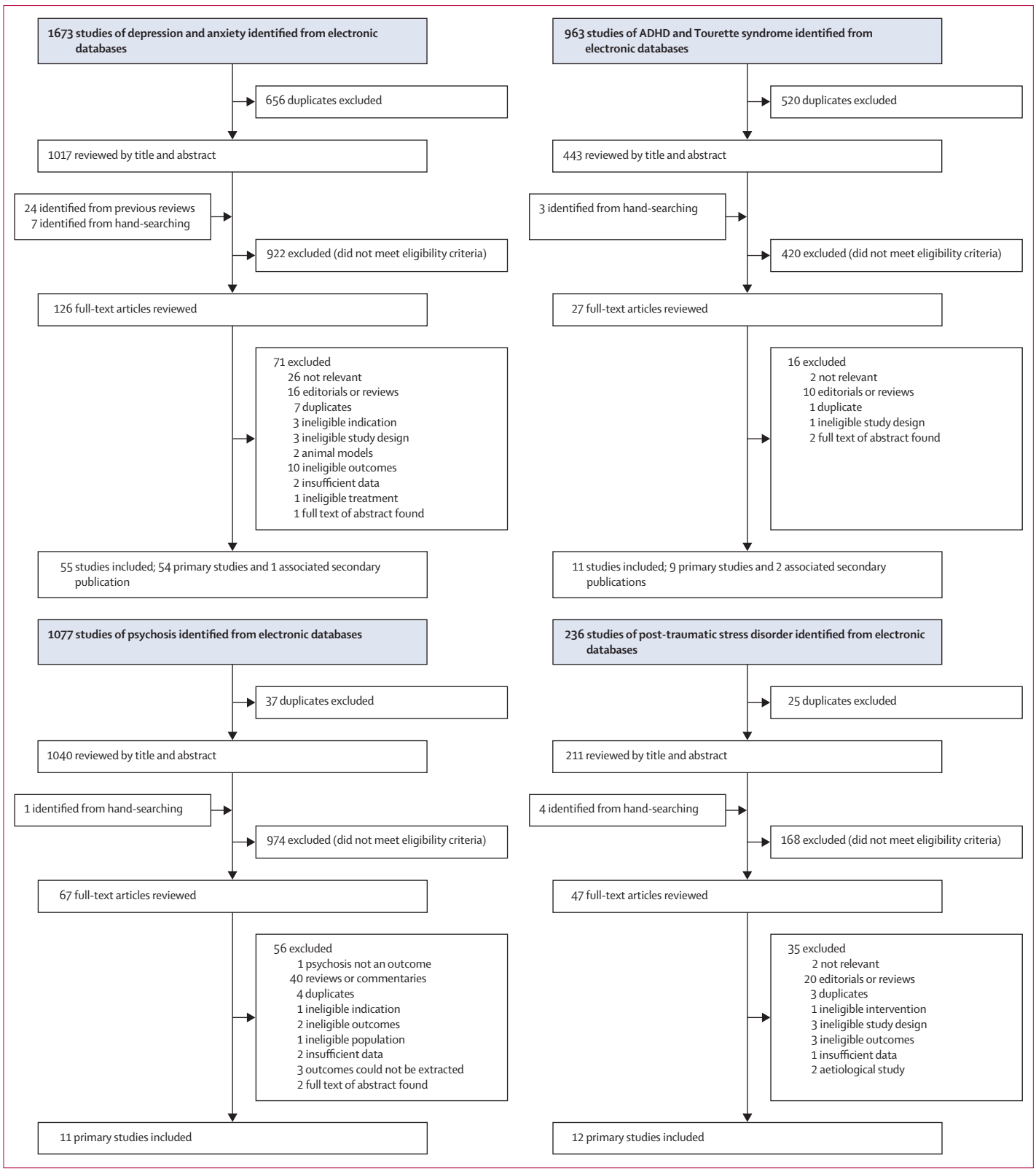

Figure: **Study selection**
ADHD=attention-deficit hyperactivity disorder.

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[19–59] (23 randomised controlled trials, including one unpublished study on EudraCT, 2012-003771-18; n=2551), 31 for anxiety[5,19–22,24,25,27,29–31,36,37,39–41,43,45,47,50,55,60–69] (17 randomised controlled trials; n=605), eight for Tourette syndrome[6,40,62,66,70–73] (two randomised controlled trials; n=36), three for ADHD[6,71,74] (one randomised controlled trial; n=30), 12 for post-traumatic stress disorder[34,67,68,75–83] (one randomised controlled trial; n=10), and 11 for psychosis[84–94] (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)
Region						
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
Year of study						
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
Conflict of interest declared?						
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
Participant characteristics						
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)
Primary health condition of study participants						
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
Primary indication						
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-naive	38·5%	71·0%	33·3%	56·3%	NR	17·2%
Number of studies with cannabinoid-naive 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^9 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[45] or placebo[20,23,36,39,40,46,47,50,52,56,58] 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[40] 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).[54]

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%),[20,36,39,40,47,50,69] with no difference seen in the single, small study that used an active comparator (table 2).[45] 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.[41,61,63] 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[40] 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).[5,60] 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.[74] No significant

	Comparator	Studies (participants)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pooled SMD (95% CI)	I^2	Favours	GRADE
Depression											
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)	..	..	..	..	..	..	..	..	..
Anxiety											
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)	..	..	..	..	..	..	..	..	..
ADHD											
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
Tourette syndrome											
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.[40,66] 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.[78] 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^2	Favours	GRADE
(Continued from previous page)											
Post-traumatic stress disorder											
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
Psychosis											
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=Δ⁹ 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.[86] 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[85,92] or active[90] 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),[92] but did not significantly improve cognitive or emotional functioning.[85,88,90,92]

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^2=59%) and withdrawals due to adverse events (2·78 [1·59 to 4·86]; 11 studies, n=1621; I^2=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^2	Favours	GRADE
Depression											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
Anxiety											
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)	..	..	..	..	..	..	..	..	..
ADHD											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
Tourette syndrome											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
Post-traumatic stress disorder											
..	..	0 (0)	..	..	..	..	..	..	..	..	..
Psychosis											
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^2	Group with more adverse events or withdrawals	GRADE
THC–CBD											
Adverse events											
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
Withdrawals											
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
CBD											
Adverse events											
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
Withdrawals											
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
Cannabis											
Adverse events											
Adverse events, all-cause	..	0 (0)	..	..	..	..	..	..	..	..	..
Serious adverse events, all-cause	..	0 (0)	..	..	..	..	..	..	..	..	..
Treatment-emergent adverse events, all-cause	..	0 (0)	..	..	..	..	..	..	..	..	..
Withdrawals											
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^9 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,[63] 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,[79,81,82] whereas one found that symptoms worsened with cannabis use in people with post-traumatic stress disorder and comorbid mental disorder.[83] We identified one open-label study where psychosis was the primary outcome, which found that CBD reduced psychosis symptoms.[93]

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.[8] 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.[11,95–99] 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.[99] 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.[95] 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[9]). 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.[13] 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.[100,101] 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.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix for

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

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Contents

PRISMA checklist

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, where it can be accessed, and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8, Appendix
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Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
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Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10, Appendix
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Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12, Appendix
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RESULTS			
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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2, 11

Appendix A: Search terms employed in the electronic databases

Please note that exemplars for the Medline strategies have been included here. Readers wishing for details of search terms for other databases are welcome to contact the study authors for details

Table A1: Medline search strategy for depression

1	cannabis.mp. or exp Cannabis/	15696
2	marijuana.mp. or exp cannabis/	20185
3	cannabinoids.mp. or exp Cannabinoids/	14269
4	endocannabinoids.mp. or exp Endocannabinoids/	5561
5	endocannabinoid.mp.	5261
6	dronabinol.mp. or exp Dronabinol/	6505
7	dronabinol.mp.	6505
8	nabilone.mp.	263
9	marinol.mp.	78
10	levonantradol.mp.	69
11	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	7859
12	cesamet.mp.	15
13	delta-9-THC.mp.	1157
14	delta-9-tetrahydrocannabinol.mp.	3178
15	nabiximols.mp.	179
16	sativex.mp.	139
17	cannabidiol.mp. or exp Cannabidiol/	1657
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	37831
19	drug therapy.mp. or exp Drug Therapy/	1261275
20	analgesics.mp. or exp Analgesics/	500492
21	prescription drugs.mp. or exp Prescription Drugs/	7696
22	analgesic drugs.mp.	2018
23	medical marijuana.mp. or exp Medical Marijuana/	957
24	medicinal marijuana.mp.	52
25	medical cannabis.mp.	156
26	medicinal cannabis.mp.	94
27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	1672943
28	factorial*.ti,ab.	21460
29	random*.ti,ab.	832076
30	(crossover* or "cross over" or cross-over*).ti,ab.	66463
31	placebo*.ti,ab.	177296
32	double blind.tw.	118616
33	single blind.tw.	10671
34	randomized controlled trial.mp. or exp Randomized controlled Trial/	468444
35	assign*.ti,ab.	235116
36	allocat*.ti,ab.	84265
37	"evaluation study".mp. or exp evaluation/	2367
38	intervention.mp.	429480
39	treatment effectiveness evaluation.mp.	9
40	prospective study.mp. or exp Prospective Studies/	494480
41	Comparative Study/	1795471
42	"comparative study".ti,ab.	61484
43	N-of-1.mp.	51391
44	Clinical trials.mp.	340838
45	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or	3653275
46	depression.mp. or exp Depression/ or exp Depression, Postpartum/ or exp Long-Term	314739
47	exp Depressive Disorder/ or exp Depressive Disorder, Major/ or major depression.mp. or	1118077
48	46 or 47	1298018
49	18 and 27 and 45 and 48	981
50	limit 49 to yr="1980 -Current"	838

Table A2: Medline search strategy for anxiety
(9th April 2018)

1	cannabis.mp. or exp Cannabis/	15696
2	marijuana.mp. or exp cannabis/	20185
3	endocannabinoids.mp. or exp Endocannabinoids/	5978
4	endocannabinoid.mp.	5216
5	dronabinol.mp. or exp Dronabinol/	6505
6	nabilone.mp.	263
7	marinol.mp.	78
8	levonantradol.mp.	69
9	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	7859
10	cesamet.mp.	15
11	delta-9-THC.mp.	1157
12	delta-9-tetrahydrocannabinol.mp.	3178
13	nabiximols.mp.	179
14	sativex.mp.	139
15	cannabidiol.mp. or exp Cannabidiol/	1657
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or	34691
17	drug therapy.mp. or exp Drug Therapy/	1261275
18	analgesics.mp. or exp Analgesics/	500492
19	prescription drugs.mp. or exp Prescription Drugs/	7696
20	analgesic drugs.mp.	2018
21	medical marijuana.mp. or exp Medical Marijuana/	957
22	medicinal marijuana.mp.	52
23	medical cannabis.mp.	156
24	medicinal cannabis.mp.	94
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1672943
26	factorial*.ti,ab.	21460
27	random*.ti,ab.	832076
28	(crossover* or "cross over" or cross-over*).ti,ab.	66463
29	placebo*.ti,ab.	177296
30	double blind.tw.	118616
31	single blind.tw.	10671
32	randomized controlled trial.mp. or exp Randomized controlled Trial/	468444
33	assign*.ti,ab.	235116
34	allocat*.ti,ab.	84265
35	"evaluation study".mp. or exp evaluation/	2367
36	intervention.mp.	429480
37	treatment effectiveness evaluation.mp.	9
38	prospective study.mp. or exp Prospective Studies/	494893
39	Comparative Study/	1795471
40	"comparative study".ti,ab.	61484
41	N-of-1.mp.	51391
42	Clinical trials.mp.	340838
43	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or	3653275
44	exp Anxiety/ or exp Performance Anxiety/ or anxiety.mp. or exp	212162
45	anxiety disorders.mp.	37367
46	social anxiety.mp.	4238
47	44 or 45 or 46	212162
48	16 and 25 and 43 and 47	149

Table A3: Medline search strategy for attention-deficit hyperactivity disorder and Tic disorder

(16th April 2018)

1	cannabis.mp. or exp Cannabis/	11056
2	marijuana.mp. or exp cannabis/	13797
3	endocannabinoids.mp. or exp Endocannabinoids/	1032
4	endocannabinoid.mp.	1941
5	dronabinol.mp. or exp Dronabinol/	93
6	nabilone.mp.	73
7	marinol.mp.	15
8	levonantradol.mp.	16
9	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	2186
10	cesamet.mp.	8
11	delta-9-THC.mp.	116
12	delta-9-tetrahydrocannabinol.mp.	866
13	nabiximols.mp.	31
14	sativex.mp.	62
15	cannabidiol.mp. or exp Cannabidiol/	498
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	20239
17	drug therapy.mp. or exp Drug Therapy/	136378
18	analgesics.mp. or exp Analgesics/	3875
19	prescription drugs.mp. or exp Prescription Drugs/	4523
20	analgesic drugs.mp.	3465
21	medical marijuana.mp. or exp Medical Marijuana/	303
22	medicinal marijuana.mp.	26
23	medical cannabis.mp.	155
24	medicinal cannabis.mp.	44
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	143664
26	factorial*.ti,ab.	17614
27	random*.ti,ab.	176306
28	(crossover* or "cross over" or cross-over*).ti,ab.	9201
29	placebo*.ti,ab.	37307
30	double blind.tw.	21383
31	single blind.tw.	1747
32	randomized controlled trial.mp. or exp Randomized controlled Trial/	14616
33	assign*.ti,ab.	87543
34	allocat*.ti,ab.	26827
35	"evaluation study".mp. or exp evaluation/	102194
36	intervention.mp.	236157
37	treatment effectiveness evaluation.mp.	21997
38	prospective study.mp. or exp Prospective Studies/	10765
39	Comparative Study/	0
40	"comparative study".ti,ab.	11351
41	N-of-1.mp.	8783
42	Clinical trials.mp.	25375
43	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or	593086
44	exp Attention Deficit Disorder with Hyperactivity/ or ADHD.mp.	27696
45	Attention Deficit Disorder.mp.	25335
46	Attention Deficit Hyperactivity Disorder.mp.	24226
47	Tourette's syndrome.mp. or exp Tourette Syndrome/	3354
48	Tic disorder.mp. or exp Tic Disorders/	537
49	44 or 45 or 46 or 47 or 48	35887
50	16 and 25 and 43 and 49	24
51	limit 50 to yr="1980 -Current"	17

Table A4: Medline search strategy for post-traumatic stress disorder
(16th April 2018)

1	cannabis.mp. or exp Cannabis/	11056
2	marijuana.mp. or exp cannabis/	13797
3	cannabinoids.mp. or exp Cannabinoids/	5300
4	endocannabinoids.mp. or exp Endocannabinoids/	1032
5	endocannabinoid.mp.	1941
6	dronabinol.mp. or exp Dronabinol/	93
7	nabilone.mp.	73
8	marinol.mp.	15
9	levonantradol.mp.	16
10	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	2186
11	cesamet.mp.	8
12	delta-9-THC.mp.	116
13	delta-9-tetrahydrocannabinol.mp.	866
14	nabiximols.mp.	31
15	sativex.mp.	62
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	21631
17	drug therapy.mp. or exp Drug Therapy/	136378
18	analgesics.mp. or exp Analgesics/	3875
19	prescription drugs.mp. or exp Prescription Drugs/	4523
20	analgesic drugs.mp.	3465
21	medical marijuana.mp. or exp Medical Marijuana/	303
22	medicinal marijuana.mp.	26
23	medical cannabis.mp.	155
24	medicinal cannabis.mp.	44
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	143664
26	factorial*.ti,ab.	17614
27	random*.ti,ab.	176306
28	(crossover* or "cross over" or cross-over*).ti,ab.	9201
29	placebo*.ti,ab.	37307
30	double blind.tw.	21383
31	single blind.tw.	1747
32	randomized controlled trial.mp. or exp Randomized controlled Trial/	14616
33	assign*.ti,ab.	87543
34	allocat*.ti,ab.	26827
35	"evaluation study".mp. or exp evaluation/	102194
36	intervention.mp.	236157
37	treatment effectiveness evaluation.mp.	21997
38	prospective study.mp. or exp Prospective Studies/	10765
39	Comparative Study/	0
40	"comparative study".ti,ab.	11351
41	N-of-1.mp.	8783
42	Clinical trials.mp.	25375
43	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or	593086
44	post-traumatic stress disorder.mp. or exp Stress Disorders, Post-Traumatic/	9356
45	Stress Disorders, Post-Traumatic.mp.	7
46	posttraumatic stress disorder.mp.	34608
47	(posttraumatic or post-traumatic).tw.	41689
48	44 or 45 or 46 or 47	44359
49	16 and 25 and 43 and 48	16
50	limit 49 to yr="1980-Current"	16

Table A5: Medline search strategy for psychosis
(7th May 2018)

1	cannabis.mp. or exp Cannabis/	15777
2	marijuana.mp. or exp cannabis/	20291
3	cannabinoids.mp. or exp Cannabinoids/	14320
4	endocannabinoids.mp. or exp Endocannabinoids/	6004
5	endocannabinoid.mp.	5246
6	dronabinol.mp. or exp Dronabinol/	6520
7	dronabinol.mp.	6520
8	nabilone.mp.	264
9	marinol.mp.	78
10	levonantradol.mp.	69
11	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	7882
12	cesamet.mp.	15
13	delta-9-THC.mp.	1158
14	delta-9-tetrahydrocannabinol.mp.	3184
15	nabiximols.mp.	180
16	sativex.mp.	140
17	cannabidiol.mp. or exp Cannabidiol/	1665
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	38004
19	drug therapy.mp. or exp Drug Therapy/	1264367
20	analgesics.mp. or exp Analgesics/	501445
21	prescription drugs.mp. or exp Prescription Drugs/	7740
22	analgesic drugs.mp.	2024
23	medical marijuana.mp. or exp Medical Marijuana/	974
24	medicinal marijuana.mp.	53
25	medical cannabis.mp.	162
26	medicinal cannabis.mp.	95
27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	1676788
28	factorial*.ti,ab.	21550
29	random*.ti,ab.	835618
30	(crossover* or "cross over" or cross-over*).ti,ab.	66676
31	placebo*.ti,ab.	177829
32	double blind.tw.	118884
33	single blind.tw.	10710
34	randomized controlled trial.mp. or exp Randomized controlled Trial/	470069
35	assign*.ti,ab.	235913
36	allocat*.ti,ab.	84713
37	"evaluation study".mp. or exp evaluation/	2386
38	intervention.mp.	431956
39	treatment effectiveness evaluation.mp.	9
40	prospective study.mp. or exp Prospective Studies/	496901
41	Comparative Study/	1797303
42	"comparative study".ti,ab.	61635
43	N-of-1.mp.	51532
44	Clinical trials.mp.	341848
45	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or	3663150
46	Schizo$.ti,ab.	115224
47	(Psychos* or Psychot*).ti,ab.	186962
48	SCHIZOPHRENIA, DISORGANIZED/ or SCHIZOPHRENIA, CATATONIC/ or	118986
49	paranoid disorders/ or psychotic disorders/	45195
50	46 or 47 or 48 or 49	311484
51	18 and 27 and 45 and 50	204
52	limit 51 to yr="1980 -Current"	195

Appendix B: Screening tables

Table B1: List of depression and anxiety studies excluded at full text review stage and reasons for exclusion

	Depression and anxiety search – excluded reference	Reason for exclusion
1.	Abraham HD, Fava M. Order of onset of substance abuse and depression in a sample of depressed outpatients. Comprehensive psychiatry 1999; 40(1): 44-50.	Wrong study design
2.	Abuhasira R, Schleider LBL, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European Journal of Internal Medicine 2018; 49: 44-50.	Irrelevant
3.	Allsop Dj CJLNDAJMMSCRGRHRMMPNMMB. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry 2014; 71(3): 281.	Wrong indication
4.	Arendt M, Rosenberg R, Fjordback L, et al. Testing the self-medication hypothesis of depression and aggression in cannabis-dependent subjects. Psychological Medicine 2007; 37(7): 935-45.	Irrelevant
5.	Arias Horcajadas F. Treatment of psychiatric disorders associated with cannabis use. Trastornos Adictivos 2011; 13(3): 113-8.	Review/commentary
6.	Aronne LJ, Finer N, Hollander PA, et al. Efficacy and safety of CP-945,598, a selective cannabinoid CB1 receptor antagonist, on weight loss and maintenance. Obesity 2011; 19(7): 1404-14.	Irrelevant
7.	Bahorik AL, Newhill CE, Eack SM. Characterizing the longitudinal patterns of substance use among individuals diagnosed with serious mental illness after psychiatric hospitalization. Addiction 2013; 108(7): 1259-69.	Irrelevant
8.	Barrowclough C, Gregg L, Lobban F, Bucci S, Emsley R. The impact of cannabis use on clinical outcomes in recent onset psychosis. Schizophrenia Bulletin 2015; 41(2): 382-90.	Wrong study design
9.	Bergamaschi MM, Chagas MHN, Chaves DI, et al. Anxiolytic effect of cannabidiol in subjects with social anxiety disorder. European Neuropsychopharmacology 2010; 20: S542.	Abstract - have full text
10.	Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-nave social phobia patients. Neuropsychopharmacology 2011; 36(6): 1219-26.	Duplicate
11.	Bergamaschi Mm QRHCMHdODCDMBSKFQJRRSNN. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2011; 36(6): 1219.	Duplicate
12.	Bhattacharyya S, Crippa JA, Martin-Santos R, et al. The effects of delta-9-tetrahydrocannabinol and cannabidiol on brain function in man. Schizophrenia Research 2012; 136: S26.	Irrelevant
13.	Bhattacharyya S, Fusar-Poli P, Borgwardt S, et al. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. Archives of general psychiatry 2009; 66(4): 442-51.	Irrelevant
14.	Bhattacharyya S F-PPBSM-SRNCOCCAPSMLFPCCJA. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. Archives of general psychiatry 2009; 66(4): 442.	Duplicate
15.	Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. The American Journal of Drug and Alcohol Abuse 2014; 40(1): 23-30.	Irrelevant
16.	Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. The American journal of psychiatry 2001; 158(12): 2033-7.	Irrelevant
17.	Bricker JB, Russo J, Stein MB, et al. Does occasional cannabis use impact anxiety and depression treatment outcomes?: Results from a randomized effectiveness trial. Depression and Anxiety 2007; 24(6): 392-8.	Irrelevant
18.	Brunt TM, Van Genugten M, Honer-Snoeken K, Van De Velde MJ, Niesink RJM. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. Journal of clinical psychopharmacology 2014; 34(3): 344-9.	Irrelevant
19.	Buechi S. Efficacy of Cannabidiol: Clinical Studies with Cannabidiol and Cannabidiol-Containing Extracts. [German]. Schweizerische Zeitschrift fur GanzheitsMedizin 2017; 29(6): 367-71.	Irrelevant
20.	Caldentey JG, Lopez-Sendon JL, Trigo P, et al. A double blind, cross over, placebo-controlled, phase II trial of sativex in huntington's disease. Journal of Neurology, Neurosurgery and Psychiatry 2012; 83: A62.	Limited data
21.	Campos AC, Brant F, Miranda AS, Machado FS, Teixeira AL. Cannabidiol increases survival and promotes rescue of cognitive function in a murine model of cerebral malaria. Neuroscience 2015; 289: 166-80.	Animal study
22.	Chan GCK, Hall W, Freeman TP, Ferris J, Kelly AB, Winstock A. User characteristics and effect profile of Butane Hash Oil: An extremely high-potency cannabis	Wrong outcomes

	Depression and anxiety search – excluded reference	Reason for exclusion
	concentrate. Drug and Alcohol Dependence 2017; 178: 32-8.	
23.	Clermont-Gnamien S, Atlani S, Attal N, Le Mercier F, Guirimand F, Brasseur L. [The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain]. Utilisation therapeutique du D9-tetrahydrocannabinol (dronabinol) dans les douleurs neuropathiques refractaires 2002; 31(39 Pt 1): 1840-5.	Irrelevant
24.	Crippa JA, Zuardi AW, Martin-Santos R, et al. Cannabis and anxiety: A critical review of the evidence. Human Psychopharmacology 2009; 24(7): 515-23.	Review/commentary
25.	Danielsson AK, Lundin A, Agardh E, Allebeck P, Forsell Y. Cannabis use, depression and anxiety: A 3-year prospective population-based study. Journal of Affective Disorders 2016; 193: 103-8.	Wrong study design
26.	De Trane S, Buchanan K, Keenan L, et al. THC: CBD (Nabiximols) has a beneficial effect on resistant MS related spasticity and reduces the need for Intrathecal baclofen. Multiple Sclerosis Journal 2017; 23 (3 Supplement 1): 1012-3.	Wrong outcomes
27.	Erbe B. [Cannabis - medicinal use]. Deutsche medizinische Wochenschrift (1946) 2014; 139(3): 74-5.	Review/commentary
28.	Forray A, Bozzo J, Cole J, Spodick J, Roberts JD. Marijuana use in adults with sickle cell disease. Drug and Alcohol Dependence 2017; 171: e64-e5.	Irrelevant
29.	Fusar-Poli P, Crippa JA, Bhattacharyya S, et al. Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Archives of general psychiatry 2009; 66(1): 95-105.	Irrelevant
30.	Fusar-Poli P APBSCJAMABSM-SRSMLOCCAZZ. Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. The international journal of neuropsychopharmacology 2010; 13(4): 421.	Irrelevant
31.	Garrido M, Charlottel L, Riba J, et al. Low abuse potential and overall subjective effects after the sublingual administration of therapeutic single doses of tetrahydrocannabinol, cannabidiol or the combination of both drugs. Basic and Clinical Pharmacology and Toxicology 2013; 113: 12-3.	Irrelevant
32.	Grant BF. Comorbidity between DSM-IV drug use disorders and major depression: results of a national survey of adults. Journal of substance abuse 1995; 7(4): 481-97.	Irrelevant
33.	Hill KP, Palastro MD, Gruber SA, et al. Nabilone pharmacotherapy for cannabis dependence: A randomized, controlled pilot study. American Journal on Addictions 2017; 26(8): 795-801.	Irrelevant
34.	Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain. Journal of Pain and Symptom Management 2010; 39(2): 167-79.	Wrong outcomes
35.	Karschner El DWDMRPLFWSGRSHMA. Subjective and physiological effects after controlled Sativex and oral THC administration. Clinical Pharmacology and Therapeutics 2011; 89(3): 400.	Irrelevant
36.	Katzman MA, Furtado M, Anand L. Targeting the Endocannabinoid System in Psychiatric Illness. Journal of clinical psychopharmacology 2016; 36(6): 691-703.	Review/commentary
37.	Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of Neurology 2013; 260(4): 984-97.	Wrong outcomes
38.	Lawn W, Freeman TP, Pope RA, et al. Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypotheses. Psychopharmacology 2016; 233(19-20): 3537-52.	Wrong outcomes
39.	Leehey M, Liu Y, Epstein C, et al. Open label study of cannabidiol in Parkinson's disease. Movement Disorders 2017; 32 (Supplement 2): 913.	Duplicate
40.	Libby AM, Orton HD, Stover SK, Riggs PD. What came first, major depression or substance use disorder? Clinical characteristics and substance use comparing teens in a treatment cohort. Addictive Behaviors 2005; 30(9): 1649-62.	Irrelevant
41.	Lynch Me C-RPHAG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of Pain and Symptom Management 2014; 47(1): 166.	Wrong outcomes
42.	Malik Z, Bayman L, Valestin J, Rizvi-Toner A, Hashmi S, Schey R. Dronabinol increases pain threshold in patients with functional chest pain: A pilot double-blind placebo-controlled trial. Diseases of the Esophagus 2017; 30 (2) (no pagination)(12455).	Duplicate
43.	Marco EM, Garcia-Gutierrez MS, Bermudez-Silva FJ, et al. Endocannabinoid system and psychiatry: In search of a neurobiological basis for detrimental and potential therapeutic effects. Frontiers in Behavioral Neuroscience 2011; (OCTOBER): no pagination.	Review/commentary
44.	Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. Endocannabinoid system and mood disorders: Priming a target for new therapies. Pharmacology and Therapeutics 2013; 138(1): 18-37.	Review/commentary
45.	Mitchell JT, Sweitzer MM, Tunno AM, Kollins SH, McClernon FJ. "I Use Weed for My ADHD": A Qualitative Analysis of Online Forum Discussions on Cannabis Use and ADHD. PLoS ONE [Electronic Resource] 2016; 11(5): e0156614.	Irrelevant
46.	Muirhead C. Marijuana and CF: Controversies associated with patient use. Pediatric Pulmonology 2015; 50: 152-4.	Review/commentary

	Depression and anxiety search – excluded reference	Reason for exclusion
47.	Muramatsu RS, Silva N, Ahmed I. Suspected dronabinol withdrawal in an elderly cannabis-naive medically Ill patient. The American journal of psychiatry 2013; 170(7): 804.	Irrelevant
48.	Naguib M, Foss JF. Medical use of marijuana: Truth in evidence. Anesthesia and Analgesia 2015; 121(5): 1124-7.	Review/commentary
49.	Nelson T, Liu YH, Bagot KS, Stein MT. Weeding out the justification for marijuana treatment in patients with developmental and behavioral conditions. Journal of Developmental and Behavioral Pediatrics 2017; 38(6): 446-8.	Irrelevant
50.	Nussbaum A, Thurstone C, Binswanger I. Medical marijuana use and suicide attempt in a patient with major depressive disorder. The American journal of psychiatry 2011; 168(8): 778-81.	Irrelevant
51.	Palmieri B, Laurino C, Vadala M. Short-term efficacy of CBD-enriched hemp oil in girls with dysautonomic syndrome after human papillomavirus vaccination. Israel Medical Association Journal 2017; 19(2): 79-84.	Duplicate
52.	Piper BJ, Dekeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. Journal of Psychopharmacology 2017; 31(5): 569-75.	Irrelevant
53.	Ruglass LM, Shevorykin A, Radoncic V, et al. Impact of cannabis use on treatment outcomes among adults receiving cognitive-behavioral treatment for PTSD and substance use disorders. Journal of Clinical Medicine 2017; 6 (2) (no pagination)(14).	Wrong outcomes
54.	Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: Depression is a major confounding factor. Diabetes Care 2010; 33(1): 128-30.	Wrong outcomes
55.	Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy. Diabetes Care 2010; 33(1): 128-30.	Duplicate
56.	Sidiropoulou K, Mamalis S, Passos ID, Pliakou E, Mironidou-Tzouveleki M. The use of cannabis and cannabinoids for medical purposes. Review of Clinical Pharmacology and Pharmacokinetics, International Edition 2017; 31(2): 120-9.	Review/commentary
57.	Sinha S, McCaul ME, Hutton HE, et al. Marijuana use and HIV treatment outcomes among PWH receiving care at an urban HIV clinic. Journal of Substance Abuse Treatment 2017; 82: 102-6.	Wrong treatment
58.	Soares VP, Campos AC. Evidences for the anti-panic actions of cannabidiol. Current Neuropharmacology 2017; 15(2): 291-9.	Review/commentary
59.	Solowij N, Broyd S, Van Hell H, et al. Opposite effects of THC and CBD on auditory mismatch negativity: A randomised controlled trial of acute cannabinoid administration. European Neuropsychopharmacology 2014; 24: S215.	Wrong indication
60.	Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. Bmj 2004; 329(7460): 253.	Wrong outcomes
61.	Todd SM, Zhou C, Clarke DJ, Chohan TW, Bahceci D, Arnold JC. Interactions between cannabidiol and DELTA9-THC following acute and repeated dosing: Rebound hyperactivity, sensorimotor gating and epigenetic and neuroadaptive changes in the mesolimbic pathway. European Neuropsychopharmacology 2017; 27(2): 132-45.	Animal study
62.	Tracy DK, Joyce DW, Shergill SS, Allsop CFHKMM. Kaleidoscope. The British Journal of Psychiatry 2014; 205(2): 166-7.	Review/commentary
63.	Turner S, Kumar R, Fairhurst C. Safety, efficacy and tolerability of oro-mucosal tetrahydrocannabinol/cannabidiol therapy to reduce spasticity in children and adolescents. results of a multicentre, double blind placebo controlled trial. Developmental Medicine and Child Neurology 2017; 59 (Supplement 4): 12-3.	Limited data
64.	Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain 2003; 102(1): 211-6.	Wrong outcomes
65.	Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association 2015; 313(24): 2456-73.	Review/commentary
66.	Williamson EM, Evans FJ. Cannabinoids in clinical practice. Drugs 2000; 60(6): 1303-14.	Review/commentary
67.	Winton-Brown TT, Allen P, Bhattacharrya S, et al. Modulation of auditory and visual processing by delta-9- tetrahydrocannabinol and cannabidiol: An fMRI study. Neuropsychopharmacology 2011; 36(7): 1340-8.	Irrelevant
68.	Wong SS, Wilens TE. Medical uses of cannabinoids in children and adolescents: A systematic review. Journal of the American Academy of Child and Adolescent Psychiatry 2017; 56 (10): S295.	Review/commentary
69.	Zhornitsky S, Potvin S. Cannabidiol in humans-The quest for therapeutic targets. Pharmaceuticals 2012; 5(5): 529-52.	Review/commentary
70.	Zuardi AW, Crippa JAS, Dursun SM, et al. Cannabidiol was ineffective for manic episode of bipolar affective disorder. Journal of Psychopharmacology 2010; 24(1): 135-7.	Wrong indication
71.	Zuardi Aw SIFEKIG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacology 1982; 76(3): 245.	Irrelevant

Table B2: List of ADHD and Tic disorder studies excluded at full text review stage and reasons for exclusion

	Reference	Reason for exclusion
1.	Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. Journal of Ethnopharmacology 2006; 105(1-2): 1-25.	Review/commentary
2.	Brunt TM, Van Genugten M, Honer-Snoeken K, Van De Velde MJ, Niesink RJM. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. Journal of clinical psychopharmacology 2014; 34(3): 344-9.	Review/commentary
3.	Cooper RE, Williams E, Seegobin S, Tye C, Asherson P. The effects of combined delta-9-tetrahydrocannabinol and cannabidiol on neurocognitive and behavioural function in attention-deficit/hyperactivity disorder. European Neuropsychopharmacology 2016; 26: S74.	Abstract - have full text
4.	Cooper RE, Williams E, Seegobin S, Tye C, Kuntsi J, Asherson P. Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. European Neuropsychopharmacology 2016; 26: S130.	Abstract - have full text
5.	Karschner EL, Darwin WD, McMahon RP, et al. Subjective and physiological effects after controlled sativex and oral THC administration. Clinical Pharmacology and Therapeutics 2011; 89(3): 400-7.	Irrelevant
6.	Katzman MA, Furtado M, Anand L. Targeting the Endocannabinoid System in Psychiatric Illness. Journal of clinical psychopharmacology 2016; 36(6): 691-703.	Review/commentary
7.	Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. Endocannabinoid system and mood disorders: Priming a target for new therapies. Pharmacology and Therapeutics 2013; 138(1): 18-37.	Review/commentary
8.	Mitchell JT, Sweitzer M, Tunno A, Hagmann C, Kollins SH, McClernon J. "Smoking pot helps me focus": A qualitative analysis of Internet forum discussions of ADHD and cannabis use. Drug and Alcohol Dependence 2015; 156: e153-e4.	Duplicate
9.	Mitchell JT, Sweitzer MM, Tunno AM, Kollins SH, Joseph McClernon F. "I use weed for my ADHD": A qualitative analysis of online forum discussions on cannabis use and ADHD. PLoS ONE 2016; 11(5): no pagination.	Wrong setting
10.	Muller-Vahl KR. Cannabinoids reduce symptoms of Tourette's syndrome. Expert Opinion on Pharmacotherapy 2003; 4(10): 1717-25.	Review/commentary
11.	Muller-Vahl KR. Treatment of Tourette syndrome with cannabinoids. Behavioural Neurology 2013; 27(1): 119-24.	Review/commentary
12.	Nelson T, Liu YH, Bagot KS, Stein MT. Weeding Out the Justification for Marijuana Treatment in Patients with Developmental and Behavioral Conditions. Journal of Developmental & Behavioral Pediatrics 2017; 38(6): 446-8.	Review/commentary
13.	Noorman K, Van Hell HH, Bossong MG, Ramsey NF, Jager G. Delta9-THC causes alterations in impulse regulation-related brain function: New insights from a pharmaco-imaging study. European Neuropsychopharmacology 2010; 20: S297-S8.	Irrelevant
14.	Turcotte D, Dorze JAL, Esfahani F, Frost E, Gomori A, Namaka M. Examining the roles of cannabinoids in pain and other therapeutic indications: A review. Expert Opinion on Pharmacotherapy 2010; 11(1): 17-31.	Review/commentary
15.	Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association 2015; 313(24): 2456-73.	Review/commentary
16.	Wilkinson ST, Radhakrishnan R, D'Souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. Journal of Clinical Psychiatry 2016; 77(8): 1050-64.	Review/commentary

Table B3: List of PTSD studies excluded at full text review stage and reasons for exclusion

	PTSD search – excluded reference	Reason for exclusion
1	Abuhasira R, Schleider LBL, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European Journal of Internal Medicine. 2018;49:44-50.	Wrong outcomes
2	Akirav I. Targeting the endocannabinoid system to treat haunting traumatic memories. 2013;7:124.	Review/commentary
3	Belendiuk KA, Baldini LL, Bonn-Miller MO. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. 2015;10(1):10.	Review/commentary
4	Betthauser K, Pilz J, Vollmer LE. Use and effects of cannabinoids in military veterans with posttraumatic stress disorder. 2015;72(15):1279-84.	Review/commentary
5	Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a potential treatment for anxiety disorders. 2015;12(4):825-36.	Review/commentary
6	Brugnatelli V. Cannabis & PTSD: the insight of a NeuroPsychiatrist.	Review/commentary
7	Calhoun PS, Sampson WS, Bosworth HB, Feldman ME, Kirby AC, Hertzberg MA, et al. Drug use and validity of substance use self-reports in veterans seeking help for posttraumatic stress disorder. 2000;68(5):923.	Wrong study design
8	Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: A retrospective evaluation. Journal of clinical psychopharmacology. 2014;34(5):559-64.	Duplicate
9	Cottler LB, Mager D. Posttraumatic stress disorder among substance users from the general population. 1992;149(5):664.	Wrong study design
10	Eaneff SD. The patient voice includes Emojis: A case study in the use of probabilistic topic modeling to characterize patient conversations in an online community of PTSD patients. Value in Health. 2017;20(5):A327.	Wrong outcomes
11	Eaneff SD. The patient voice includes Emojis: A case study in the use of probabilistic topic modeling to characterize patient conversations in an online community of PTSD patients. Value in Health. 2017;20 (5):A327.	Duplicate
12	Fattore L, Piva A, Zanda MT, Fumagalli G, Chiamulera C. Psychedelics and reconsolidation of traumatic and appetitive maladaptive memories: focus on cannabinoids and ketamine. Psychopharmacology. 2017:1-13.	Review/commentary
13	Haney M, Evins AE. Does cannabis cause, exacerbate or ameliorate psychiatric disorders? An oversimplified debate discussed. 2016;41(2):393-401.	Review/commentary
14	Hill MN, Campolongo P, Yehuda R, Patel S. Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder. Neuropsychopharmacology. 2018;43(1):80-102.	Review/commentary
15	Katzman MA, Furtado M, Anand L. Targeting the Endocannabinoid System in Psychiatric Illness. Journal of clinical psychopharmacology. 2016;36(6):691-703.	Review/commentary
16	Kerbage H, Richa S. Non-antidepressant long-term treatment in post-traumatic stress disorder (PTSD). 2015;10(2):116-25.	Review/commentary
17	Korem N, Zer-Aviv TM, Ganon-Elazar E, Abush H, Akirav I. Targeting the endocannabinoid system to treat anxiety-related disorders. 2016;27(3):193-202.	Review/commentary
18	Krumm BA. Cannabis for posttraumatic stress disorder: A neurobiological approach to treatment. 2016;41(1):50-4.	Review/commentary
19	Lao N, Ganesh V, Zhang L, Drost L, Wan BA, Blake A, et al. Symptom clusters in patient reported outcomes with medical cannabis. Supportive Care in Cancer. 2017;25(2 Supplement 1):S61.	Wrong outcomes
20	Loflin M, Earleywine M, Bonn-Miller M. Medicinal versus recreational cannabis use: Patterns of cannabis use, alcohol use, and cued-arousal among veterans who screen positive for PTSD. 2017;68:18-23.	Irrelevant
21	Loflin MJE, Babson KA, Bonn-Miller MO. Cannabinoids as therapeutic for PTSD. 2017;14:78-83.	Review/commentary
22	Neumeister A. The endocannabinoid system provides an avenue for evidence-based treatment development for PTSD. 2013;30(2):93-6.	Review/commentary
23	Neumeister A, Normandin MD, Pietrzak RH, Piomelli D, Zheng M-Q, Gujarro-Anton A, et al. Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study. 2013;18(9):1034-40.	Etiological study
24	Neumeister A, Seidel J, Ragen BJ, Pietrzak RH. Translational evidence for a role of endocannabinoids in the etiology and treatment of posttraumatic stress disorder. 2015;51:577-84.	Review/commentary
25	Pietrzak RH, Huang Y, Corsi-Travali S, Zheng M-Q, Lin S-f, Henry S, et al. Cannabinoid type 1 receptor availability in the amygdala mediates threat processing in trauma survivors. 2014;39(11):2519-28.	Etiological study
26	Rabinak C, Peters C, Elrahal F, Milad M, Rauch S, Phan KL, Greenwald M. Cannabinoid facilitation of fear extinction in posttraumatic stress disorder. Neuropsychopharmacology. 2017; 43(Supplement 1): S339.	No data reported

	PTSD search – excluded reference	Reason for exclusion
27	Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral DELTA9-tetrahydrocannabinol in chronic post-traumatic stress disorder. Clinical drug investigation. 2014;34(8):587-91.	Duplicate
28	Ruglass LM, Shevorykin A, Radoncic V, Smith KMZ, Smith PH, Galatzer-Levy IR, et al. Impact of cannabis use on treatment outcomes among adults receiving cognitive-behavioral treatment for PTSD and substance use disorders. Journal of Clinical Medicine. 2017;6(2):no pagination.	Wrong intervention
29	Ruglass LM, Shevorykin A, Radoncic V, Smith KMZ, Smith PH, Galatzer-Levy IR, et al. Impact of cannabis use on treatment outcomes among adults receiving cognitive-behavioral treatment for PTSD and substance use disorders. Journal of Clinical Medicine. 2017;6 (2) (no pagination)(14).	Irrelevant
30	Tull MT, McDermott MJ, Gratz KL. Marijuana dependence moderates the effect of posttraumatic stress disorder on trauma cue reactivity in substance dependent patients. 2016;159:219-26.	Wrong study design
31	Valentiner D, Wyman S. More study needed on possible role of pot in psychotherapy The jury is still out on use of cannabis to treat PTSD and anxiety disorders.	Review/commentary
32	Wilkinson ST, Radhakrishnan R, D'Souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. Journal of Clinical Psychiatry. 2016;77(8):1050-64.	Review/commentary
33	Wong SS, Wilens TE. Medical uses of cannabinoids in children and adolescents: A systematic review. Journal of the American Academy of Child and Adolescent Psychiatry. 2017;56 (10):S295.	Review/commentary
34	Yarnell S. The Use of Medicinal Marijuana for Posttraumatic Stress Disorder: A Review of the Current Literature. 2014;17(3).	Review/commentary
35	Zer-Aviv TM, Segev A, Akirav I. Cannabinoids and post-traumatic stress disorder: clinical and preclinical evidence for treatment and prevention. 2016;27(7):561-9.	Review/commentary

Table B4: List of psychosis studies excluded at full text review stage and reasons for exclusion

	Psychosis search – excluded reference	Reason for exclusion
1	Alexander SPH. Therapeutic potential of cannabis-related drugs. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2016;64:157-66.	Review/commentary
2	Andrade C. Cannabis and neuropsychiatry, 1: Benefits and risks. Journal of Clinical Psychiatry. 2016;77(5):e551-e4.	Review/commentary
3	Anonymous. Cannabis-based medications—GW pharmaceuticals: high CBD, high THC, medicinal cannabis—GW pharmaceuticals, THC:CBD. Drugs in R&D. 2003;4(5):306-9.	Review/commentary
4	Appiah-Kusi E, Mondelli V, McGuire P, Bhattacharyya S. Effects of cannabidiol treatment on cortisol response to social stress in subjects at high risk of developing psychosis. Psychoneuroendocrinology. 2016;71 (Supplement 1):23-4.	Wrong outcomes
5	Archie S, Boydell KM, Stasiulis E, Volpe T, Gladstone BM. Reflections of young people who have had a first episode of psychosis: What attracted them to use alcohol and illicit drugs? Early intervention in psychiatry. 2013;7(2):193-9.	Outcomes cannot be extracted
6	Arias Horcajadas F. Treatment of psychiatric disorders associated with cannabis use. [Spanish]. Trastornos Adictivos. 2011;13(3):113-8.	Review/commentary
7	Ashton CH. Biomedical benefits of cannabinoids? Addiction Biology. 1999;4(2):111-26.	Wrong indication
8	Ashton CH, Moore PB. Endocannabinoid system dysfunction in mood and related disorders. Acta Psychiatrica Scandinavica. 2011;124(4):250-61.	Review/commentary
9	Baandrup L, Ostrup Rasmussen J, Klokker L, Austin S, Bjornshave T, Fuglsang Bliksted V, et al. Treatment of adult patients with schizophrenia and complex mental health needs - A national clinical guideline. Nordic Journal of Psychiatry. 2016;70(3):231-40.	Review/commentary
10	Bhattacharyya S. Cannabidiol as a treatment in different stages of psychosis-efficacy and mechanisms. Schizophrenia Bulletin. 2018;44 (Supplement 1):S27.	Review/commentary
11	Bhattacharyya, S., Wilson, R., Allen, P., Bossong, M., Appiah-Kusi, E., McGuire, P. (2018). Effect of cannabidiol on symptoms, distress and neurophysiological abnormalities in clinical high-risk for psychosis patients: a placebo controlled study. Schizophrenia Bulletin, 44(Supplement 1):S28.	Abstract- have full text
12	Boggs DL, Gupta A, D'Souza DC, Bielen K, Thurnauer H, Nhundu V, et al. Cannabinoid receptor antagonist treatment of cognitive dysfunction in schizophrenia. Journal of Pharmacy Practice. 2015;28(3):321.	Duplicate
13	Bumb JM, Enning F, Leweke FM. Drug repurposing and emerging adjunctive treatments for schizophrenia. Expert Opinion on Pharmacotherapy. 2015;16(7):1049-67.	Review/commentary
14	Capasso A, Sobarzo-Sanchez E, Nabavi SF, Rastrelli L. Cannabinoids for the treatment of schizophrenia: An overview. Current Topics in Medicinal Chemistry. 2016;16(17):1916-23.	Review/commentary
15	Chan GCK, Hall W, Freeman TP, Ferris J, Kelly AB, Winstock A. User characteristics and effect profile of Butane Hash Oil: An extremely high-potency cannabis concentrate. Drug and Alcohol Dependence. 2017;178:32-8.	Outcomes cannot be extracted
16	Costa B. On the pharmacological properties of DELTA ⁹-tetrahydrocannabinol (THC). Chemistry and Biodiversity. 2007;4(8):1664-77.	Review/commentary
17	Crippa JA. The paradox of cannabis sativa: The plant that can induce psychotic symptoms and also treat them. Schizophrenia Research. 2012;(Supplement 1):S26.	Review/commentary
18	Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802.	Review/commentary
19	Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. Journal of psychopharmacology (Oxford, England). 2013;27(1):19-27.	Wrong patient population
20	Fakhoury M. Could cannabidiol be used as an alternative to antipsychotics? Journal of Psychiatric Research. 2016;80:14-21.	Review/commentary
21	Garay RP, Citrome L, Samalin L, Liu CC, Thomsen MS, Correll CU, et al. Therapeutic improvements expected in the near future for schizophrenia and schizoaffective disorder: An appraisal of phase III clinical trials of schizophrenia-targeted therapies as found in US and EU clinical trial registries. Expert Opinion on Pharmacotherapy. 2016;17(7):921-36.	Review/commentary
22	Garay RP, Samalin L, Hameg A, Llorca PM. Investigational drugs for anxiety in patients with schizophrenia. Expert Opinion on Investigational Drugs. 2015;24(4):507-17.	Review/commentary
23	Hahn B. The Potential of Cannabidiol Treatment for Cannabis Users with Recent-Onset Psychosis. Schizophrenia Bulletin. 2018;44(1):46-53.	Review/commentary
24	Hjorthoj C. Cannabis use in patients with psychosis-current and future state of affairs. Early intervention in psychiatry. 2012;6 (SUPPL.1):6.	Review/commentary
25	Iseger TA, Bossong MG. A systematic review of the antipsychotic properties of cannabidiol in humans. Schizophrenia Research. 2015;162(1-3):153-61.	Review/commentary
26	Kaur R, Ambwani SR, Singh S. Endocannabinoid system: A multi-facet therapeutic target. Current Clinical Pharmacology. 2016;11(2):110-7.	Review/commentary
27	Khoury JM, Neves MDCLD, Roque MAV, Queiroz DADB, Correa de Freitas AA, de Fatima A, et al. Is there a role for cannabidiol in psychiatry? World Journal of Biological Psychiatry. 2017:1-16.	Review/commentary
28	Kolliakou A, Sallis H, Joseph C, O'Connor J, Gayer-Anderson C, Falcone AM, et al. Reasons for cannabis use in firstepisode psychosis. Schizophrenia Bulletin. 2013;1):S294.	Duplicate
29	Leweke FM, Mueller JK, Lange B, Rohleder C. Therapeutic potential of cannabinoids in psychosis. Biological Psychiatry. 2016;79(7):604-12.	Review/commentary
30	Leweke M. The endocannabinoid system in schizophrenia-a mechanistically new approach to its pathophysiology and treatment. Schizophrenia Bulletin. 2013;39(21).	Full text not available

	Psychosis search – excluded reference	Reason for exclusion
31	Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clinical Psychopharmacology and Neuroscience. 2017;15(4):301-12.	Review/commentary
32	Marco EM, Garcia-Gutierrez MS, Bermudez-Silva FJ, Moreira FA, Guimaraes F, Manzanares J, et al. Endocannabinoid system and psychiatry: In search of a neurobiological basis for detrimental and potential therapeutic effects. Frontiers in Behavioral Neuroscience. 2011.	Review/commentary
33	McGuire P, Robson P, Cubala W, Vasile D, Morrison P, Barron, R, Taylor A, Wright S. A randomized controlled trial of cannabidiol in schizophrenia. Schizophrenia Bulletin. 2018;44(Supplement 1):S27	Abstract- have full text
34	McLoughlin BC, Pushpa-Rajah JA, Gillies D, Rathbone J, Variend H, Kalakouti E, et al. Cannabis and schizophrenia. Cochrane Database of Systematic Reviews. 2014;2014 (10) (no pagination)(CD004837).	Review/commentary
35	Osborne AL, Solowij N, Weston-Green K. A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia. Neuroscience and Biobehavioral Reviews. 2017;72:310-24.	Review/commentary
36	Pierre JM. Psychosis associated with medical marijuana: Risk vs. benefits of medical cannabis use. The American Journal of Psychiatry. 2010;167(5):598-9.	Psychosis not an outcome
37	Potvin S, Stip E, Roy JY. Schizophrenia and addiction: An evaluation of the self-medication hypothesis [French]. Encephale. 2003;29(3):193-203.	Review/commentary
38	Pushpa-Rajah J, McLoughin B, Gilles D. Cannabis and schizophrenia: A Cochrane review. European Archives of Psychiatry and Clinical Neuroscience.2015;265(SUPPL. 1):S70-S1.	Review/commentary
39	Pushpa-Rajah J, McLoughin B, Gilles D. Cannabis and schizophrenia: A Cochrane review. European Archives of Psychiatry and Clinical Neuroscience. 2015;1):S70-S1.	Duplicate
40	Pushpa-Rajah JA, McLoughlin BC, Gillies D, Rathbone J, Variend H, Kalakouti E, et al. Cannabis and Schizophrenia. Schizophrenia Bulletin. 2015;41(2):336-7.	Review/commentary
41	Ranganathan M, D'Souza D, Cortes-Briones J, Skosnik, P. Efficacy of cannabidiol in the treatment of early psychosis. Schizophrenia Bulletin. 2018; 44(Supplement 1):S27	Insufficient data
42	Rathbone J, Variend H, Mehta H. Cannabis and schizophrenia. Cochrane Database of Systematic Reviews. 2008;(3) (no pagination)(CD004837).	Review/commentary
43	Renard J, Norris C, Rushlow W, Laviolette SR. Neuronal and molecular effects of cannabidiol on the mesolimbic dopamine system: Implications for novel schizophrenia treatments. Neuroscience and Biobehavioral Reviews. 2017;75:157-65.	Review/commentary
44	Rohleder C, Muller JK, Lange B, Leweke FM. Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence. Frontiers in Pharmacology. 2016;7 (NOV) (no pagination)(422).	Review/commentary
45	Roser P, Haussleiter IS. Antipsychotic-like effects of cannabidiol and rimonabant: systematic review of animal and human studies. Current Pharmaceutical Design. 2012;18(32):5141-55.	Review/commentary
46	Rubino T, Zamberletti E, Parolaro D. Endocannabinoids and mental disorders. Handbook of Experimental Pharmacology. 2015;231:261-83.	Review/commentary
47	Saito A, Ballinger MDL, Pletnikov MV, Wong DF, Kamiya A. Endocannabinoid system: Potential novel targets for treatment of schizophrenia. Neurobiology of Disease. 2013;53:10-7.	Review/commentary
48	Schubart CD, Sommer IEC, Fusar-Poli P, de Witte L, Kahn RS, Boks MPM. Cannabidiol as a potential treatment for psychosis. European Neuropsychopharmacology. 2014;24(1):51-64.	Review/commentary
49	Spencer C. Motives that maintain cannabis use among individuals with psychotic disorders. 2004:166-85.	Review/commentary
50	Test MA, Wallisch LS, Allness DJ, Ripp K. Substance use in young adults with schizophrenic disorders. Schizophrenia Bulletin. 1989;15(3):465-76.	Outcomes cannot be extracted
51	van der Meer F, Velthorst E. Course of cannabis use and clinical outcome in patients with non-affective psychosis: A 3-year follow-up study. Psychological Medicine. 2015;45(9):1977-88.	Wrong outcomes
52	Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association. 2015;313(24):2456-73.	Review/commentary
53	Wilkinson ST, Radhakrishnan R, D'Souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. Journal of Clinical Psychiatry. 2016;77(8):1050-64.	Review/commentary
54	Zhornitsky S, Potvin S. Cannabidiol in humans-The quest for therapeutic targets. Pharmaceuticals. 2012;5(5):529-52.	Review/commentary
55	Zuardi AW, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, et al. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. Current Pharmaceutical Design. 2012;18(32):5131-40.	Review/commentary
56	Zuardi AW, Crippa JAS, Hallak JEC, Pinto JP, Chagas MHN, Rodrigues GGR, Dursun SM, Tumas V. Cannabidiol for the treatment of psychosis in Parkinson's disease. European Neuropsychopharmacology. 2008; 18(Supplement 4):S417-18.	Duplicate

Appendix C: Incomplete and ongoing trials

Table C1: Ongoing trials for anxiety and depression

Principal investigator (trial ID and estimated completion)	Study design (status)	Title and purpose	Intervention(s) and comparator (s)
Agar, M. (ACTRN12616000516482) **Estimated date of completion: not provided**	Non-randomised, single-blind study (Active, recruiting)	Phase I/II, dose ranging study of the pharmacokinetics dose-response parameters, and feasibility of vaporised botanical cannabis flower bud in advanced cancer "*The primary purpose of this trial is to evaluate whether a vaporised form of medicinal cannabis is feasible and effective in increasing appetite in cancer patients with anorexia.*"	**Intervention(s):** - Bedrobinol (8-50mg/day, which is the equivalent of 1.08-6.75mg THC/day) **Comparator(s):** - Placebo leaf (18-50mg)
Amminger, G. P. (ACTRN12617000825358) **Estimated date of completion: not provided**	Open-label trial (Active, recruiting)	The cannabidiol youth anxiety pilot study (CAPS): a 12-week open- label pilot study of the safety, tolerability and efficacy of cannabidiol for anxiety disorders *"The aim of the present study is to produce preliminary evidence for the safety and anxiolytic effects of CBD in youth with anxiety disorders."*	**Intervention(s):** - Cannabidiol (200-800mg/day) **Comparator(s):** None
Baas, J. M. P. (EudraCT: 2014-004094-17) **Estimated date of completion: not provided**	Randomised, double-blind study (Active, ongoing)	Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias. *"To test the hypothesis that administration of cannabidiol as an augmentation step in combination with exposure therapy can strengthen treatment outcome in patients with phobic disorders (generalized social anxiety and panic disorder with agoraphobia) who do not respond satisfactorily to treatment as usual."*	**Intervention(s):** - Cannabidiol **Comparator(s):** - Placebo
Copeland, J. (ACTRN12616001001482p) **Estimated date of completion: not provided**	Randomised, parallel, double-blind study (Not yet recruiting)	Cannabidiol (CBD) for Cannabis and Mood Disorders in Adolescence (CCAMDA) *"The primary objectives of the study is to examine the safety and efficacy of cannabidiol (CBD) in the management of mood disorders in adolescent/young adult males with concurrent cannabis use, in a randomised controlled study. Specifically, the study will assess the impact of CBFD on mood treatment outcomes and retention rates, the quantity and frequency of cannabis use, and the impact of CBD on neurobiological markers associated with CBD response."*	**Intervention(s):** - Cannabidiol (800mg/day) **Comparator(s):** - Placebo
Davidson, E. (NCT02283281) **Estimated date of completion: February 2017**	Randomised, parallel, quadruple-blind study (Unknown)	Anesthetic Premedication With a Cannabis Extract (Cannapremed) "*…to carry out an investigation in order to re-evaluate the issue of perioperative cannabis use through a sufficiently powered and controlled clinical trial. Some of cannabis effects such as sedation, bronchodilation, dryness of respiratory secretions, vein dilation, and increase of heart rater without producing hypertension, make of it an attractive option for pre-medication; while its antiemetic properties and its analgesic potential without causing respiratory depression may be profitable for the post-operative period."*	**Intervention(s):** - Sativex (high dose: 21.6mg THC and 20mg CBD) - Sativex (low dose: 10.8mg THC and 10mg CBD) **Comparator(s):** - Acetaminophen (1g in a 50mL vial) - Midazolam (2mg in a 2mL syringe) - Placebo
Gilman, J. M. (NCT03224468)	Randomised, parallel, double-	Effect of Medical Marijuana on Neurocognition and Escalation of Use (MMNE)	**Intervention(s):** - Medical marijuana

Estimated date of completion: March 2022	blind study (Active, recruiting)	"*This study will use a randomized controlled design to test whether patients who use medical marijuana, compared to a waitlist control group, experience a change in health outcomes (relief of symptoms, or adverse health outcomes such as new-onset symptoms of cannabis use disorders, neurocognitive impairments) or brain-based changes*"	**Comparator(s):** - Waitlist control
Gruber, S. (NCT02548559) **Estimated date of completion: June 2019**	Open-label trial (Active, recruiting)	Sublingual Cannabidiol for Anxiety *"This study evaluates the effects of cannabidiol (CBD) for the treatment of anxiety in adults. Participants will use a sublingual (under-the-tongue) tincture of whole plant derived CBD three times daily for four weeks in addition to their normal treatment regimen. Participants' clinical state will be assessed weekly during the treatment period. In addition, cognitive function and measures of quality of life, sleep, and general health will be assessed at baseline and the post-treatment final visit."*	**Intervention(s):** - Cannabidiol (30mg) **Comparator(s):** None
Hardy, J. (ACTRN12618001205224) **Estimated date of completion: October 2019**	Open-label study (Active, recruiting)	A study investigating safety, dosing and effectiveness of medicinal cannabis for symptom relief for patients with advanced cancer *"It is hoped that this research will be effective in determining a safe and effective dose for symptom relief in patients with advanced cancer."*	**Intervention(s):** - CBD (600mg) - THC (30mg) **Comparator(s):** - None
Hardy, J. (ACTRN12618001220257) **Estimated date of completion: May 2022**	Randomised, parallel, quadruple-blind study (Active, not yet recruiting)	A study that evaluates the effectiveness of oral medicinal cannabis for people with advanced cancer experiencing a range of symptoms. *"It is hoped that this research will show a positive effect of CBD on symptoms for patients suffering with advanced cancer and thus provide an option in helping manage symptoms."*	**Intervention(s):** - CBD (600mg) **Comparator(s):** - Placebo
Hardy, J. (ACTRN12619000037101) **Estimated date of completion: May 2022**	Randomised, parallel, quadruple-blind study (Active, not yet recruiting)	A study that evaluates the effectiveness of oral combined THC/CBD for people with advanced cancer experiencing a range of symptoms. *"It is hoped that this research will show a positive effect of THC/CBD on symptoms for patients suffering with advanced cancer and thus provide an option in helping manage symptoms."*	**Interventions(s):** - THC (30mg)/CBD (30mg) **Comparator(s):** - Placebo
Martin, J. (ACTRN12619000265178) **Estimated date of completion: April 2023**	Open-label trial (Active, not yet recruiting)	Cannabinoids for Symptom Control in Advanced Cancer, an Open Label Prospective Clinical Trial in New South Wales (NSW) *"This is an open label study to profile how advanced cancer patients use a range of cannabis medicines for symptom relief via the collection of prospective data on open label product, dose, efficacy, safety, pharmacokinetics and pharmacodynamics to provide preliminary safety, tolerability and efficacy evidence to guide future studies."*	**Intervention(s):** - THC (30mg/day) **Comparator(s):** - None
Ranganathan, M. (NCT03206463) **Estimated date of completion: July 2019**	Randomised, cross-over, quadruple-blind study (Active, not recruiting)	Cognitive and Psychophysiological Effects of Delta-9-Tetrahydrocannabinol in Bipolar Disorder (THC-BD) *"The overarching goal of this study is to characterize the acute cognitive and psychophysiological effects of the main psychoactive constituent of cannabis, 9-delta-tetrahydrocannabinol (THC) in individuals with euthymic bipolar disorder (BD), and to begin probing the mechanisms that may underlie its effects in this illness."*	**Intervention(s):** - THC (4mg) - THC (2mg) **Comparator(s):** - Placebo
Seppi, K. (NCT03769896) **Estimated date of completion: December 2019**	Randomised, parallel, quadruple-blind study (Active, recruiting)	Nabilone for Non-motor Symptoms in Parkinson's Disease (NMS-Nab) *"This is a randomized placebo-controlled, double-blind, parallel-group, enriched enrollment randomized withdrawal study assessing the efficacy and safety of nabilone for non-motor symptoms in patients with Parkinson´s Disease. Nabilone is an analogue of tetrahydrocannabinol (THC), the psychoactive component of cannabis. Nabilone acts as a*	**Intervention(s):** - Nabilone (0.25mg) **Comparator(s):** - Placebo

		partial agonist on both Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) receptor in humans and therefore mimics the effect of THC but with more predictable side effects and less euphoria."	
Van Ameringen, M. (NCT03549819) **Estimated date of completion: October 2020**	Randomised, parallel, triple-blind study (Active, not yet recruiting)	Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot Study *"This proposed study aims to evaluate the efficacy of daily Cannabidiol (CBD) Oil Capsules in treating symptoms of DSM-5 anxiety disorders, using a two-arm, 8-week randomized, placebo-controlled trial in adults aged 21-65 years. The study will also evaluate the relationship between inflammation, anxiety and CBD using biological markers as well as examine the neuro-cognitive effects of CBD treatment."*	**Intervention(s):** - Cannabidiol (200-800mg/day) **Comparator(s):** - Placebo
Wilsey, B. (NCT02460692) **Estimated date of completion: May 2020**	Randomised, parallel, triple-blind study (Active, recruiting)	Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain *"The present study is designed to assess whether treatment with vaporized cannabis or dronabinol (oral Δ9-THC) reduces spontaneous and evoked pain more than placebo, and whether there are any differences between the two active treatments in terms of interference with activities of daily living. This study also aims to examine the effects of vaporized whole plant cannabis and dronabinol on mood, neuropsychological function, and psychomimetic side-effects (high, stoned, etc.) compared to placebo and to each other. In addition, we plan to examine the acute effects (after receiving stable treatment for 4 weeks) of vaporized cannabis and dronabinol compared to placebo and each other on driving skills."*	**Intervention(s):** - Vaporised cannabis (3.7% THC/5.6% CBD) **Comparator(s):** - Dronabinol - Placebo

Table C2: Ongoing trials for PTSD

Principal investigator (trial ID and estimated completion)	Study design (status)	Title and purpose	Intervention(s) and comparator (s)
Bonn-Miller, M. (NCT02759185) **Date of completion: January 2019**	Randomised, cross-over, triple-blind pilot study (Completed, results pending)	Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With PTSD "*The purpose of this study is to find out if cannabis can reduce PTSD symptoms in 76 military veterans with treatment-resistant PTSD. Four different types of smoked cannabis will be evaluated using a "triple-blind" cross-over placebo controlled design."*	**Intervention(s):** - High THC Marijuana (contains more THC than CBD) (1.8g/day) - High CBD Marijuana (contains more CBD than THC) (1.8g/day) - High THC/High CBD Marijuana (contains equal amounts of THC and CBD) (1.8g/day) **Comparator(s):** - Placebo cannabis
Elrahal, F. (NCT03008005) **Estimated date of completion: 31 December 2019**	Randomised, parallel, double-blind study (Active, recruiting).	Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD: R61 Study "*The goal of this study is to look at how a type of drug called cannabinoids are related to the processing of fear signals, the experience of emotions and fear, and the pattern of activity in the brain that is involved in these processes and how this relates to the development of post-traumatic stress disorder (PTSD). PTSD is an anxiety disorder that occurs after experiencing a traumatic event(s) and is characterized by unwanted memories of the trauma(s) through flashbacks or nightmares, avoidance of situations that remind the person of the event, difficulty experiencing emotions, loss of interest in activities the person used to enjoy, and increased arousal, such as difficulty falling asleep or staying asleep, anger and hypervigilance. The information gained from this study could lead to the development of new treatments for persons who suffer from anxiety or fear-based disorders*."	**Intervention(s):** Dronabinol Cap (5mg) Dronabinol Cap (10mg) **Comparator(s):** Placebo
Haney, M. (NCT03251326)	Randomised, cross-over, double-blind	Effects of Nabilone on Trauma Related Cue Reactivity in Cannabis Users With PTSD	**Intervention(s):** - Nabilone (4mg)

Estimated date of completion: August 2019	study (Active, not recruiting)	"*Despite the prevalence of cannabis use among the PTSD population and self-reports that it is used to help cope with PTSD symptoms, the direct effects of cannabis on PTSD symptomology are unknown. The purpose of this placebo-controlled, within-subject study is to assess the effects of smoked cannabis and orally administered nabilone, a synthetic analog of THC, the primary psychoactive component of cannabis on multiple dimensions of PTSD symptomatology in cannabis smokers with PTSD.*"	- Cannabis (0.0 and 5.6% THC) **Comparator(s):** - Propranolol (40mg) - Placebo
Loflin, M. J. (NCT03518801) **Estimated date of completion: September 2023**	Randomised, parallel, quadruple-blind study (Active, recruiting)	Cannabidiol and Prolonged Exposure (CBD-PE) *"The trial will include a randomized control trial to evaluate the efficacy of using Cannabidiol (CBD), a non-intoxicating cannabinoid, as an adjunctive to Prolonged Exposure therapy (PE). The trial will compare PE + CBD to PE + placebo in a sample of 136 military Veterans with PTSD at the VA San Diego Medical Center."*	**Intervention(s):** - Prolonged exposure and cannabidiol **Comparator(s):** - Prolonged exposure and placebo
Lucas, P. (NCT02517424) **Estimated date of completion: June 2020**	Randomised, cross-over, triple-blind study (Active, recruiting)	Evaluating Safety and Efficacy of Cannabis in Participants With Chronic Posttraumatic Stress Disorder "*The purpose of this study is to evaluate the safety and efficacy of vaporized cannabis in participants with chronic, treatment-resistant posttraumatic stress disorder*."	**Intervention(s):** - High THC/Low CBD Cannabis (2g per day) - High THC/High CBD Cannabis (2g per day) **Comparator(s):** - Low THC/Low CBD Cannabis (2g per day)
Marmar, C. (NCT03248167) **Estimated date of completion: August 2019**	Randomised, parallel, double-blind study (Active, not yet recruiting)	Cannabidiol as a Treatment for AUD Comorbid With PTSD "*This project aims to determine whether cannabidiol (CBD), a compound derived from the cannabis plant, is effective in treating alcohol use disorder (AUD) in individuals with comorbid posttraumatic stress disorder (PTSD)."*	**Intervention(s):** - Cannabidiol (400mg/day) **Comparator(s):** - Placebo
Rabinak, C. A. (NCT02069366) **Estimated date of completion: December 2019**	Parallel, randomised, double-blind (Active, recruiting)	Cannabinoid Control of Fear Extinction Neural Circuits in Post-traumatic Stress Disorder "*The goal of this study is to look at how a type of drug called cannabinoids are related to the processing of fear signals, the experience of emotions and fear, and the pattern of activity in the brain that is involved in these processes and how this relates to the development of post-traumatic stress disorder (PTSD). PTSD is an anxiety disorder that occurs after experiencing a traumatic event(s) and is characterized by unwanted memories of the trauma(s) through flashbacks or nightmares, avoidance of situations that remind the person of the event, difficulty experiencing emotions, loss of interest in activities the person used to enjoy, and increased arousal, such as difficulty falling asleep or staying asleep, anger and hypervigilance. The information gained from this study could lead to the development of new treatments for persons who suffer from anxiety or fear-based disorders*."	**Intervention(s)** Dronabinol (7.5mg) **Comparator(s)** Placebo
Shalev, A. Y. (NCT00965809) **Estimated date of completion: April 2013**	Randomised, parallel, triple-blind study (Unknown)	Add on Study on Δ9-THC Treatment for Posttraumatic Stress Disorders (PTSD) (THC_PTSD) "*The aim of the proposed study is to broaden the previous observations and to measure the extent to which Δ 9-THC will bring to significant improvement on the full spectrum of PTSD symptoms."*	**Intervention(s):** - THC (5mg, twice a day) **Comparator(s):** - Placebo (twice a day)

Table C3: Ongoing trials for ADHD and Tics/Tourette's syndrome

Principal investigator (trial ID and estimated completion)	Study design (status)	Title and purpose	Intervention(s) and comparator (s)
Asherson, P. (NCT02249299) **Estimated date of completion: December 2015**	Randomised, parallel, quadruple-blind study (Unknown)	Experimental Medicine in ADHD - Cannabinoids (EMA-C) "*Adult patients with ADHD commonly report an improvement in behavioural symptoms when using cannabis with some reporting a preference towards cannabis over their ADHD stimulant medication. The EMA-C study aims to investigate the effects of a cannabis based medication, Sativex Oromucosal Spray on behaviour and cognition in adults with ADHD.*"	**Intervention(s):** - Sativex Oromucosal Spray (Each 100 microlitre spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD)) **Comparator(s):** - Placebo
Landeros, A. (NCT03066193) **Estimated date of completion: January 2019**	Open-label, non-randomised trial (Unknown)	Efficacy of a Therapeutic Combination of Dronabinol and PEA for Tourette Syndrome *"The investigators propose a 12-week, investigator-initiated, open-label trial of a therapeutic combination of Dronabinol and PEA in 18 adults with Tourette syndrome. Participants will receive Dronabinol and PEA in combination for the duration of the trial. The goal for this pilot study is to (1) provide initial safety, feasibility and tolerability data on both Dronabinol and PEA in a TS population and (2) provide data in order to make a more informed decision regarding the appropriate sample size and design of a larger clinical trial to prove efficacy (i.e. sample size and trial duration in large efficacy trial of the Dronabinol/PEA combination in TS)."*	**Intervention(s):** - Dronabinol (10mg) + Palmitoylethanolamide (2x400mg) **Comparator(s):** - None
Mosley, P. (ACTRN12618000545268) **Estimated date of completion: August 2020**	Randomised, cross-over, quadruple-blind study (Active, recruiting)	A Randomised, Double Blind, Placebo-Controlled Trial of Medicinal Cannabis in Adults with Tourette's Syndrome *"There is some early evidence to support the effectiveness of cannabinoids in TS, but well-designed clinical trials have yet to be conducted.* *We plan to use an oral formulation of medicinal cannabis containing two cannabinoids: tetrahydrocannabinol and cannabidiol. This formulation does not intoxicate or cause the unpleasant psychiatric effects of 'street' cannabis."*	**Intervention(s):** - THC (5mg/mL) and CBD (5mg/mL) **Comparator(s):** - Placebo
Muller-Vahl, K. R. (2016-000564-42; NCT03087201) **Estimated date of completion: May 2019**	Randomised, parallel, quadruple-blind study (Ongoing; restarted)	A randomized multi-centre double-blind placebo controlled trial to demonstrate the efficacy and safety of nabiximols in the treatment of adults with chronic tic disorders (CANNA-TICS) *"To demonstrate that treatment with the cannabis extract nabiximols is superior to placebo in reducing tics and comorbidities in patients with Tourette syndrome and chronic tic disorders."*	**Intervention(s):** - Sativex (27mg/mL THC and 25mg/mL CBD) **Comparator(s):** - Placebo
Muller-Vahl, K. (NCT03651726) **Estimated date of completion: November 2019**	Randomised, parallel, triple-blind study (Active, not yet recruiting)	A Study to Examine the Efficacy of a Therapeutic THX-110 for Tourette Syndrome *"This study evaluates the efficacy and safety of THX-110 in the management of tics and other symptoms (e.g. rage attacks, anxiety, depression, sleep difficulties) in patients with Tourette syndrome. In the first part of the study, half of the patients will receive THX-110, while the other half will receive a placebo. After completion of the first study part, patients will have the opportunity to continue into the second part of the study. In this part, all participants will receive THX-110."*	**Intervention(s):** - THX (Dronabinol (10mg) + PEA (2x400mg)) **Comparator(s):** - Placebo
Sandor, P. (NCT03247244)	Randomised, crossover, triple-	Safety and Efficacy of Cannabis in Tourette Syndrome	**Intervention(s):** - Cannabis A (THC 10%, CBD <0.5%)

Estimated date of completion: May 2019	blind study (Active, recruiting)	*"…However, there have been no controlled trials of inhaled medical cannabis for TS to date. Furthermore, various medical cannabis products are authorized in Canada with different contents of THC and cannabidiol (CBD), another primary cannabinoid. No data exists regarding the dosing, efficacy and safety of these products in the treatment of TS. To gather such data, a double-blind, randomized, crossover pilot trial will be conducted to compare the efficacy and safety of three vaporized medical cannabis products with different THC and CBD contents, as well as placebo, in adults with TS. As well, the PK/PD profile of THC and CBD of the products will be assessed and correlated with tic symptoms"*	- Cannabis B (THC 8.6%, CBD 8.6%) - Cannabis C (THC 0.6%, CBD 14%) **Comparator(s):** - Placebo

Table C4: Ongoing trials for psychosis

Principal investigator (trial ID and estimated completion)	Study design (status)	Title and purpose	Intervention(s) and comparator (s)
Hahn, B. (NCT03883360) **Estimated date of completion: June 2024**	Randomised, parallel, quadruple-blind study (Active, not yet recruiting)	Effects of Cannabidiol on Psychiatric Symptoms, Cognition, and Cannabis Consumption in Cannabis Users With Recent-Onset Psychosis *"A large proportion of people with a schizophrenia-spectrum disorder, especially in the early stages of the disease, regularly consume cannabis. Cannabis use is associated with poor prognostic outcome; however, there are no effective interventions targeted at reducing cannabis use or its deleterious effects in this population. The present trial is designed to test whether cannabidiol (CBD), a cannabinoid whose effects are in many ways antagonistic to those of Δ9-tetrahydrocannabinol (THC), can reduce psychiatric symptoms, cognitive deficits, and cannabis use in people with recent-onset psychosis who regularly consume cannabis."*	**Intervention(s):** - Cannabidiol (600mg p.o) **Comparator(s):** - Placebo
Fuchs, S. (2012-004335-23) **Estimated date of completion: not provided**	Randomised, parallel, double-blind study (Temporarily halted – Germany; Ongoing - Denmark)	A four-week, multicentre, double-blinded, randomised, active- and placebo-controlled, parallel-group trial investigating efficacy and safety of cannabidiol in acute, early-stage schizophrenic patients *"Evaluation of the efficacy of cannabidiol in alleviating the positive, negative and general symptoms of schizophrenia compared to olanzapine and placebo."*	**Intervention(s):** - Cannabidiol (20mg) **Comparator(s):** - Olanzapine (15mg) **-** Placebo
Leweke, F. M. (NCT00309413) **Date of completion: July 2008**	Randomised, cross-over, quadruple-blind study (Completed, results pending)	A Clinical Trial on the Antipsychotic Properties of Cannabidiol "*The purpose of this study is to determine whether cannabidiol, a herbal cannabinoid, is effective in the treatment of acute schizophrenic or schizophreniform psychosis in a placebo-controlled, randomized double-blind study."*	**Intervention(s):** - Cannabidiol (600mg/day) **Comparator(s):** - Placebo (600mg/day)
Leweke, F. M. (NCT02088060) **Estimated date of completion: December 2021**	Randomised, parallel, quadruple-blind study (Active, not recruiting)	A Four-week Clinical Trial Investigating Efficacy and Safety of Cannabidiol as a Treatment for Acutely Ill Schizophrenic Patients *"…In a controlled clinical trial of cannabidiol versus amisulpride (an established antipsychotic) in acute paranoid schizophrenics the investigators showed a significant clinical improvement in all symptoms of schizophrenia compared to baseline with either treatment. But cannabidiol displayed a significantly superior side-effect profile. This study is to evaluate the efficacy and safety of this novel treatment option in comparison to placebo and olanzapine, an established second generation antipsychotic in the treatment of acute schizophrenia and schizophrenia maintenance therapy, in a four-week clinical trial."*	**Intervention(s):** - Cannabidiol (2x200mg twice a day) **Comparator(s):** - Olanzapine (15mg once a day) **-** Placebo (twice a day)
Leweke, F. M. (NCT02926859)	Randomised, parallel, quadruple-	Enhancing Recovery in Early Schizophrenia	**Intervention(s):** - Cannabidiol (2x200mg

Estimated date of completion: March 2019	blind study (Recruiting)	*"…This study is to evaluate the efficacy and safety of the novel compound cannabidiol in the maintenance treatment of schizophrenia in comparison to placebo as an add-on to an established treatment with either amisulpride, aripiprazole, olanzapine, quetiapine or risperidone, in a 12-months, double-blind, parallel-group, randomized, placebo-controlled clinical trial."*	twice a day) **Comparator(s):** - Placebo (2x200mg twice a day)
McGuire, P. (NCT02006628) **Date of completion: January 2015**	Randomised, parallel, quadruple-blind study (Completed, results pending changes)	A Study of GWP42003 as Adjunctive Therapy in the First Line Treatment of Schizophrenia or Related Psychotic Disorder "*A study to compare the change in symptom severity in patients with schizophrenia or related psychotic disorder when treated with GWP42003 or placebo, added to existing anti-psychotic therapy over a period of six weeks. Secondary objectives are to evaluate the effect of GWP42003 on quality of life and cognition and to assess the safety and tolerability of GWP42003*."	**Intervention(s):** - GWP42003 (5mL containing 500mg CBD taken twice daily) **Comparator(s):** - Placebo (5mL taken twice daily)
Ranganathan, M. (NCT02102113) **Estimated date of completion: April 2019**	Randomised, cross-over, double-blind study (Active, recruiting)	Probing the Cannabinoid System in Individuals With a Family History of Psychosis *"The overall purpose of this study is to determine whether a family history of psychosis is associated with an altered cannabinoid system. This will be tested by studying individuals with and without a family history of psychosis and comparing their responses to delta 9-tetrahydrocannabinol (THC), a probe of the cannabinoid system. We hypothesize, that compared to controls with no family history of psychoses, individuals with a family history of psychoses will have an altered response to THC."*	**Intervention(s):** - THC (0.010mg/kg or 0.018mg/kg) **Comparator(s):** - Placebo
Ranganathan, M. (NCT02504151) **Estimated date of completion: December 2019**	Randomised, cross-over, quadruple-blind study (Active, not recruiting)	Cannabidiol Treatment in Patients with Early Psychosis "*The investigators hypothesize that treatment with CBD will result in: 1) Improvement evidenced by a reduction in scores on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), 2) Improvement evidenced by a reduction in the Clinical Global Impression of Severity scale (CGI); Secondary Hypothesis: 1) Greater improvement in functioning as measured on the "Patient Assessment of Own Functioning Inventory: (PAOFI) and the Quality of Life Scale (QLS)"*	**Intervention(s):** - Cannabidiol **Comparator(s):** - Placebo

Appendix D: Risk of bias assessments in included studies

Table D1: Risk of bias criteria for assessing RCTs

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing lots; minimisation
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not forsee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly forsee assignments because one of the following methods was used: used open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or no described in sufficient detail to allow a definite judgement
3. Blinding of participants and providers (performance bias) – objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding or participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
4. Blinding of participants and providers (performance bias) – subjective outcomes	Low risk	Blinding of participants and providers ensured and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by the lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
5. Blinding of outcome assessor (detection bias) – objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that that the blinding could have been broken
	High risk	No blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
6. Blinding of outcome assessor	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;

(detection bias) – subjective outcomes		Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically-relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically-relevant impact on observed effect size; Missing data have been imputed using appropriate methods; All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat).
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group).
8. Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk	Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear risk	Insufficient information to permit judgement of low or high risk.

Depression studies

Figure D1. RCTs risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

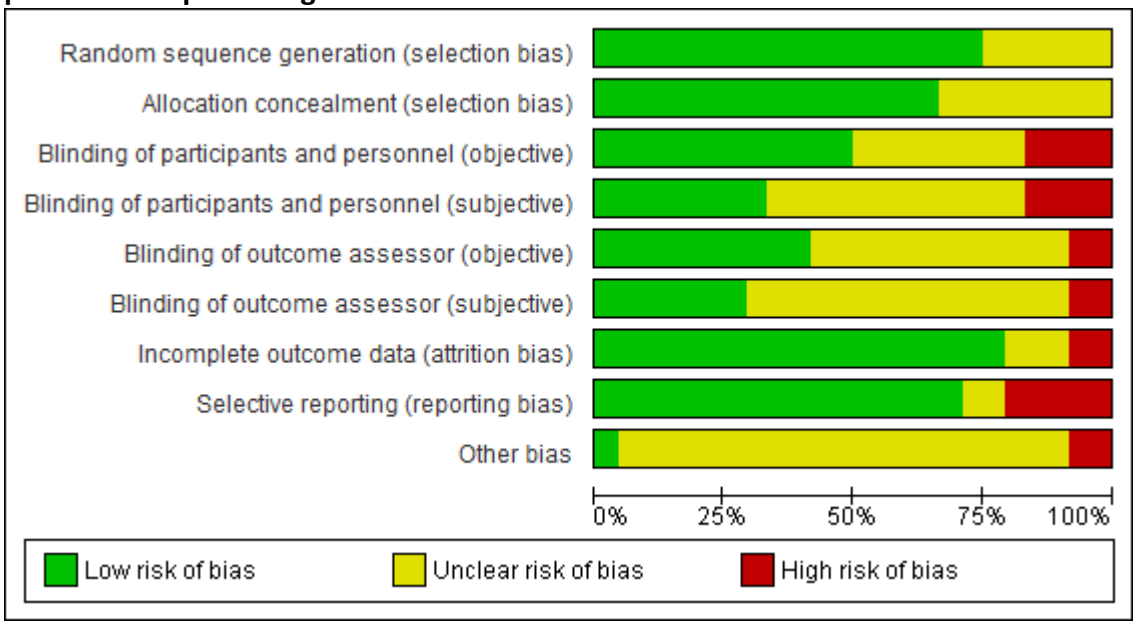
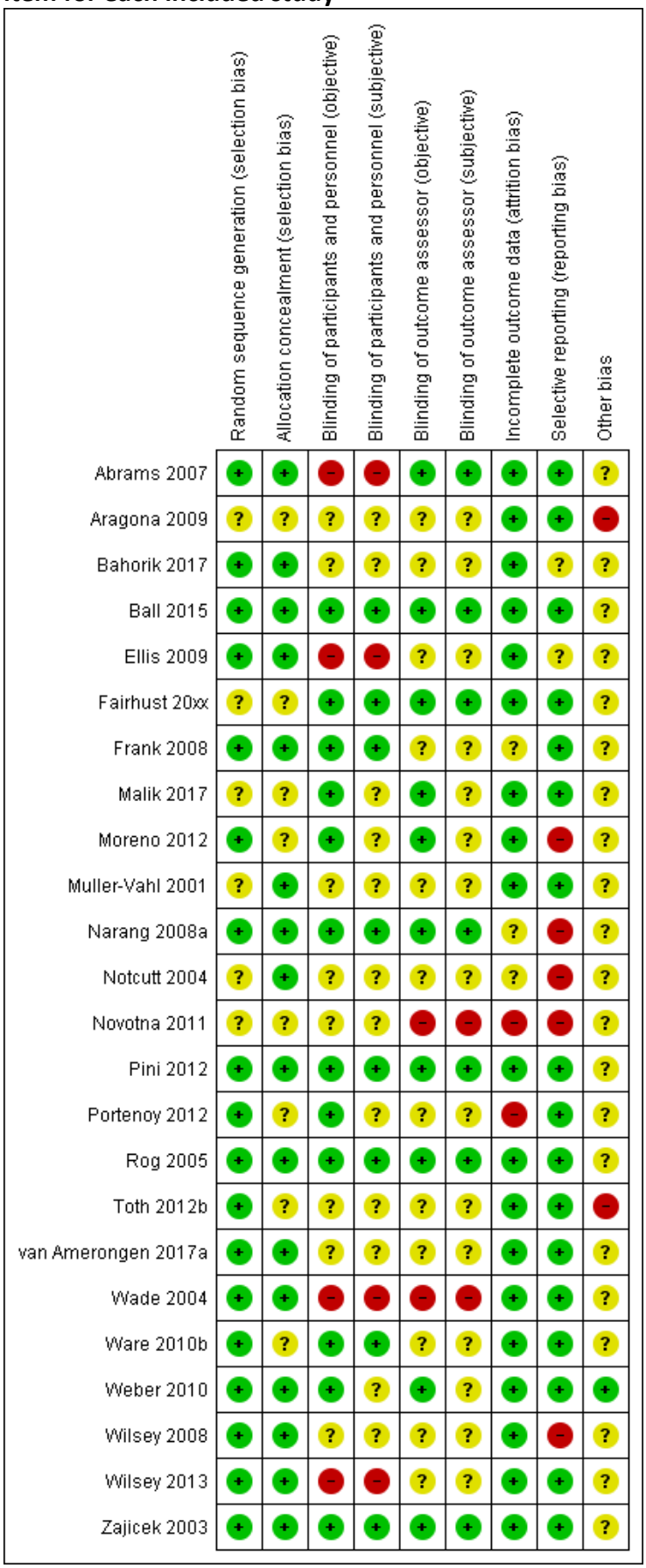


Figure D2. RCTs risk of bias summary: review authors' judgements about each risk of bias item for each included study



Anxiety studies

Figure D4: RCTs risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

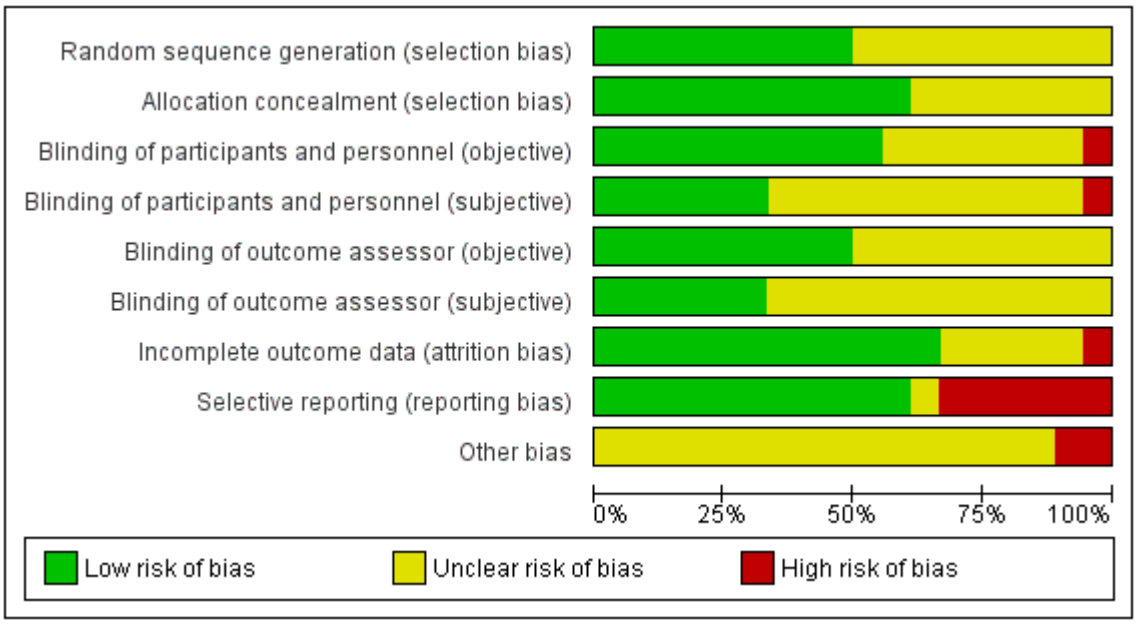
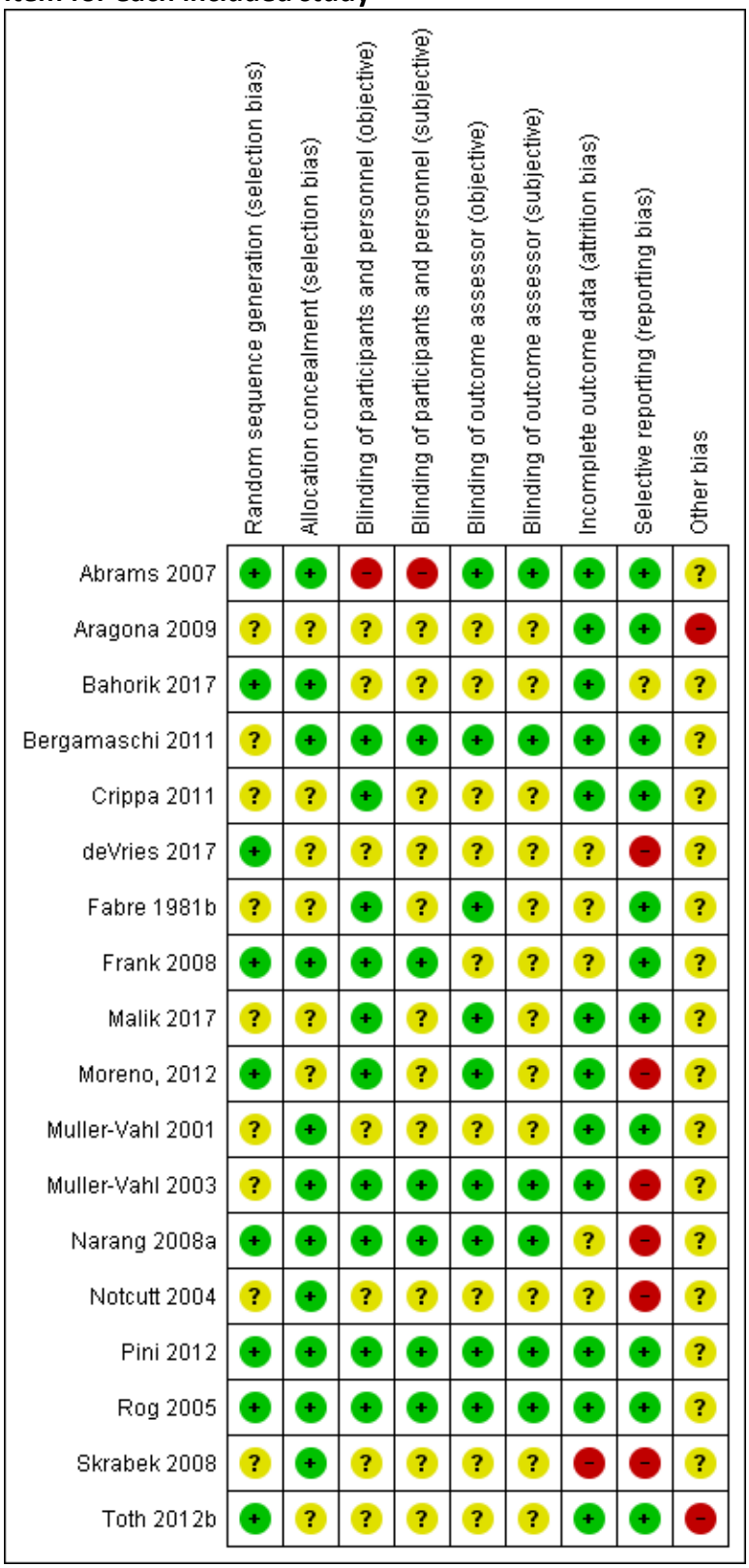


Figure D5: RCTs risk of bias summary: review authors' judgements about each risk of bias item for each included study



Tic/Tourette's disorder studies

Figure D7: RCTs risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

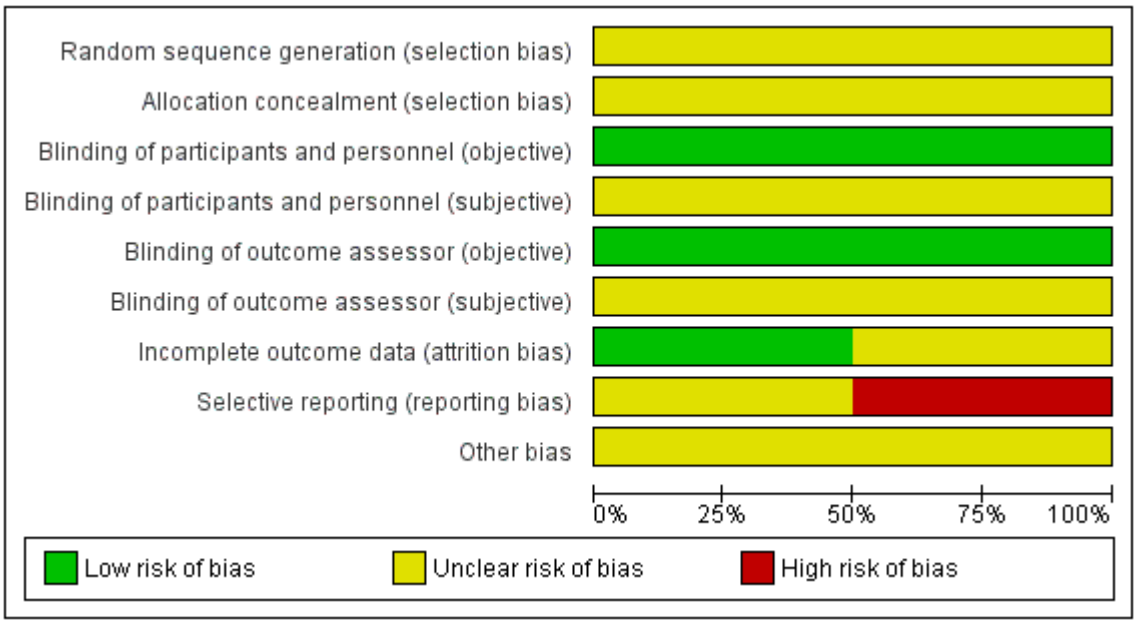
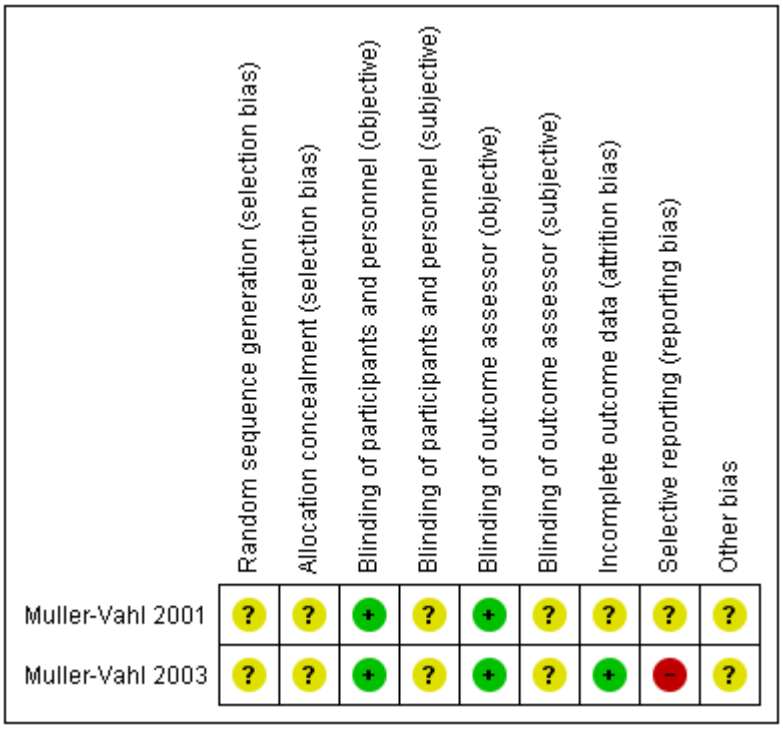


Figure D8: RCTs risk of bias summary: review authors' judgements about each risk of bias item for each included study



Attention deficit hyperactivity disorder studies

Figure D10: RCTs risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

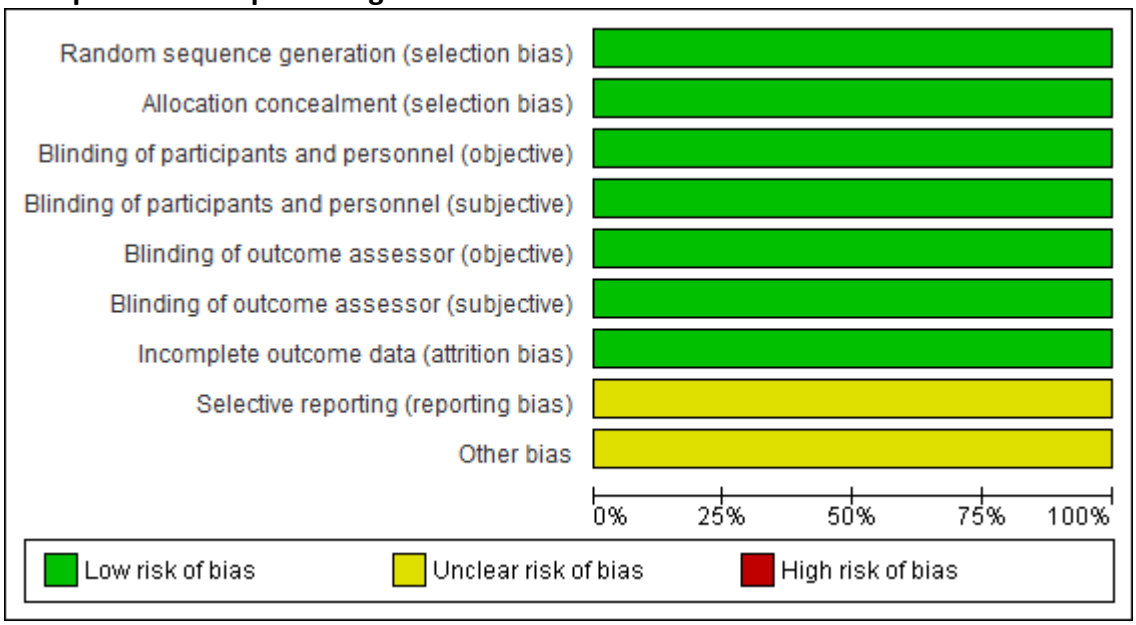
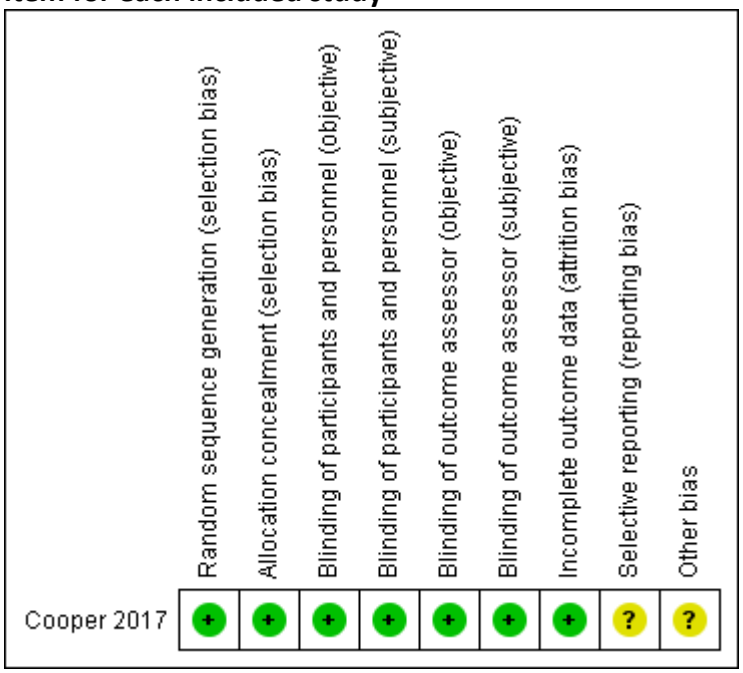


Figure D11: RCTs risk of bias summary: review authors' judgements about each risk of bias item for each included study



Post-traumatic stress disorder studies

Figure D13: RCTs risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

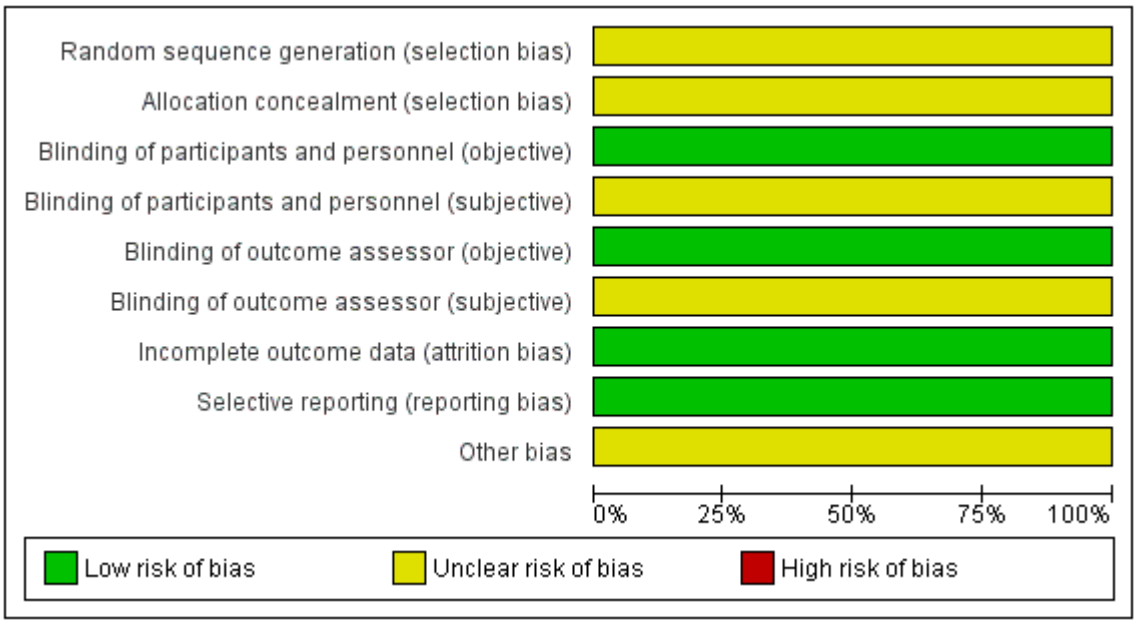


Figure D14: RCTs risk of bias summary: review authors' judgements about each risk of bias item for each included study

Psychosis studies

Figure D16: RCTs risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

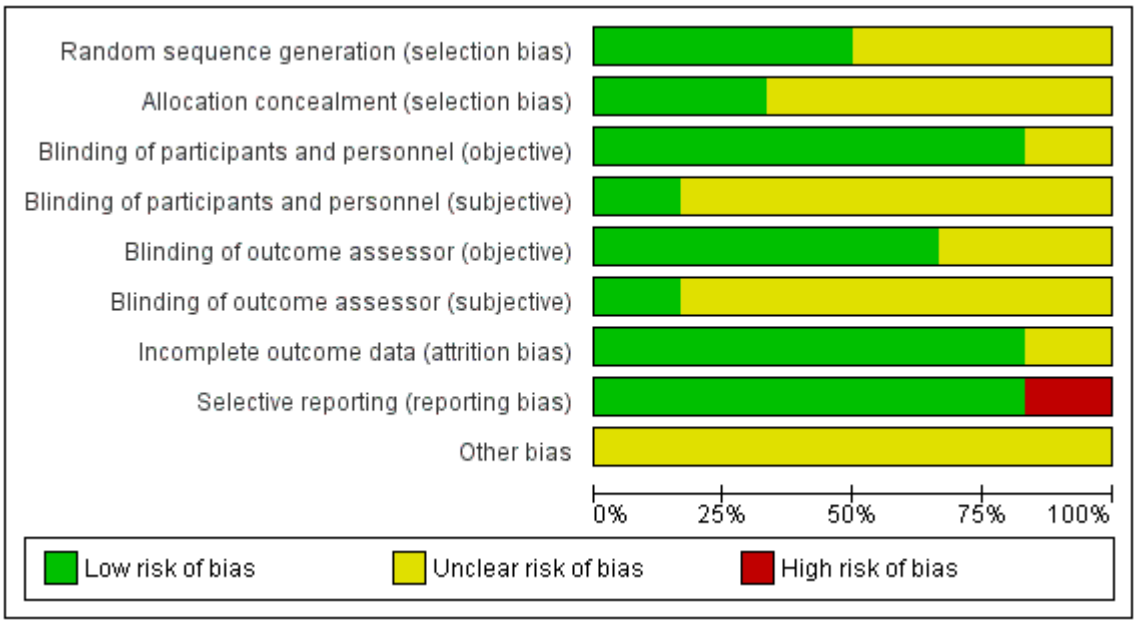
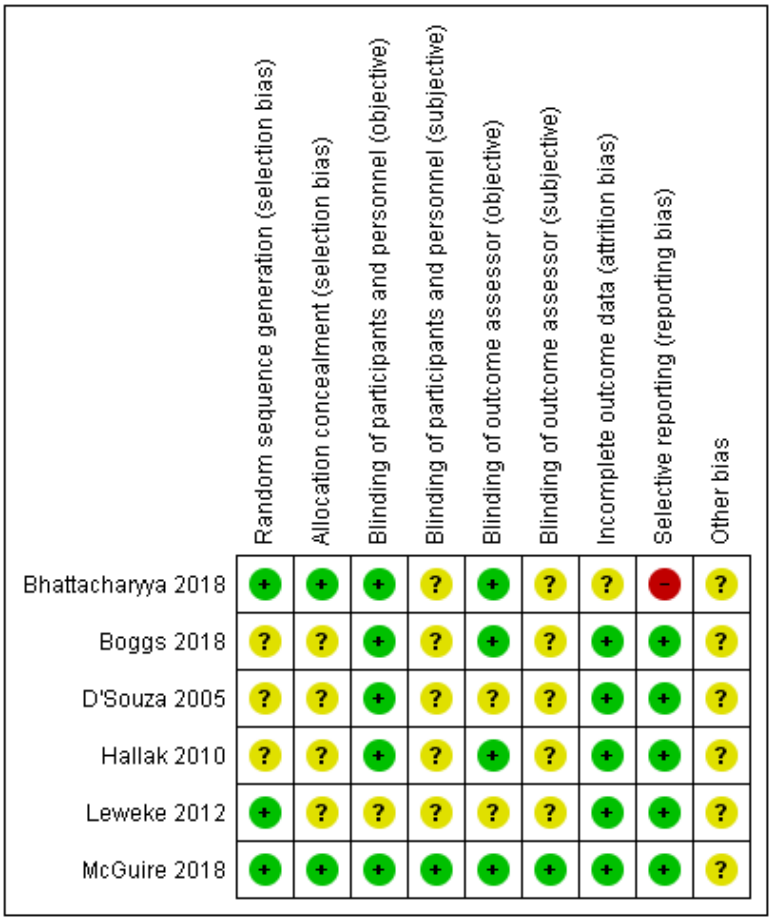


Figure D7: RCTs risk of bias summary: review authors' judgements about each risk of bias item for each included study



Appendix E: Descriptive summary of all included observational studies and RCTs

Table E1: Summary of eligible studies of cannabis and cannabinoids studies for the treatment of mental health

	Depression	Anxiety	ADHD	Tic/Tourette's disorder	PTSD	Psychosis
	N=42[1]	N=31[2]	N=3	N=8	N=12	N=11
Study design **Randomised controlled trials (RCTs)**						
Parallel RCT	10	9	1	1	-	5
Crossover RCT	13	8	-	1	1	1
Observational studies						
Open label trial	7	5	-	-	2	1
Prospective cohort study	3	3	-	-	2	1
Cross-sectional/retrospective study	5	3	1	2	1	2
Chart review	2	1	-	-	3	-
Case study/series	4	4	1	4	3	1

[1] Narang, 2008[1] and Toth, 2012[2] contributed both a RCT and observational study component

[2] Fabre, 1981[3] and Toth, 2012[2] contributed both a RCT and observational study componen

Table E2: Characteristics of included randomised controlled trials of cannabis and cannabinoids for the treatment of mental health

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Comparator	Treatment duration	Daily dose (lower and upper limits)	Outcomes included in quantitative synthesis[a]
DEPRESSION									
Abrams 2007[4] (USA)	Parallel RCT	Total N = 55 Age = 48.5 (6.5) Male % = 85.7	Analgesic and impact on mental health outcomes	Adjuvant	Cannabis sativa (smoked)	Placebo	Five days	3.56% THC	--
Aragona 2009[5] (Italy)	Crossover RCT	Total N = 17 Age = 49.8 (6.64) Male % = 35.3	Antispasticity and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Three weeks	22.14mg THC and 20.5mg CBD	DE-P2
Ball 2015[6] (UK)	Parallel RCT	Total N = 493 Age = 52.19 (7.8) Male % = 40.8	Antispasticity, analgesic, and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	Placebo	156 weeks	15.085mg (14-28 mg)	DE-P2
Ellis 2009[7] (USA)	Crossover RCT	Total N = 34 Age = 49.1 (6.9) Male % = 97	Analgesic and impact on mental health outcomes	Adjuvant	Cannabis sativa (smoked)	Placebo	Five days	NR (1-8% THC)	--
Fairhurst, unpublished[8] (UK, Israel, Czech Republic)	Parallel RCT	Total N = 72 Age = NR Male % = 61	Antispasticity, pain, quality of life and impact on mental health	Adjuvant	Nabiximols (oromucosal spray)	Placebo	12 weeks	2.7mg THC and 2.5mg CBD	DE-P2
Frank 2008[9] (UK)	Crossover RCT	Total N = 96 Age = 50.15 (13.69) Male % = 52	Analgesic and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Active: dihydrocodeine	Six weeks	NR (0.25-2mg)	--
Malik 2017[10] (USA)	Parallel RCT	Total N = 19 Age = 43 (NR) Male % = 15.4	Analgesic and impact on mental health outcomes	NR	Dronabinol (oral)	Placebo	Four weeks	10mg	DE-P2
Moreno 2016[11] (Spain)	Crossover RCT	Total N = 25 Age = 47.6 (12.4) Male % = 56	Motor symptoms associated with Huntington's Disease, cognitive symptoms, and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Twelve weeks	NR (2.7-32.4mg THC and 2.5-30mg)	DE-P2
Müller-Vahl 2001[12] (Germany)	Crossover RCT	Total N = 12 Age = 34 (13) Male % = 91.7	Tic severity associated with Tourette's syndrome, quality of life, and impact on mental health outcomes	Adjuvant	THC extract	Placebo	One day	7.083mg (5-10mg)	DE-P2
Narang 2008a[1] (USA)	Crossover RCT	Total N = 30 Age = 43.76 (11.8) Male % = 46.7	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	Placebo	One day	1) 10mg 2) 20mg	--
Notcutt 2004[13] (UK)	Crossover RCT	Total N = 34 Age = 46.7 (NR) Male % = 32	Analgesic and impact on mental health outcomes	NR	THC extract; CBD extract; THC:CBD extract (sublingual spray)	Placebo	Eight weeks	2.5mg THC; 2.5mg CBD; 2.5mg:2.5mg THC:CBD	--
Novotna 2011[14] (18 centres in UK, 11 in Spain, 10 in Poland, 8 in Czech Republic, 5 in Italy)	Parallel RCT	Total N = 241 Age = 48.6 (9.33) Male % = 40	Antispasticity and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Twelve weeks	22.41mg THC + 20.75mg CBD (max 32.4mg THC+30mg CBD)	--
Pini 2012[15] (Italy)	Crossover RCT	Total N = 30 Age = 52.7 (9.6) Male % = 33.3	Analgesic and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Active: ibuprofen	Eight weeks	0.5mg	DE-P2
Portenoy 2012[16] (Multicentre—North America, Europe, Latin America and South Africa)	Parallel RCT	Total N = 360 Age = 58 (12.2) Male % = 51.7	Analgesic, quality of life, and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Five weeks	1) NR (2.7-10.8mgTHC and 2.5-10mg CBD) 2) NR (16.2-17mg THC and 15-25mg CBD) 3) NR (29.7-43.2mg THC, 27.5-40mg CBD)	DE-P2
Rog 2005[17] (UK)	Parallel RCT	Total N = 66 Age = 49.2 (8.3) Male % = 21.2	Analgesic and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Four weeks	25.92mg THC (5.4-67.5mg) and 24mg CBD (5-62.5mg)	DE-P2
Toth 2012b[2] (Canada)	Parallel RCT	Total N = 26 Age = 61.2 (14.95) Male % = 53.8	Analgesic, quality of life, and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Placebo	Four weeks	2.24mg (1-4mg)	DE-P2
van Amerongen 2017[18] (Netherlands)	Crossover RCT	Total N = 24 Age = 54.3 (8.9) Male % = 33.3	Analgesic and impact on mental health outcomes	Adjuvant	THC extract (oral)	Placebo	NR	16mg	--
Wade 2004[19] (UK)	Parallel RCT	Total N = 160 Age = 50.7 (NR) Male % = 38	Antispasticity, analgesic, and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Six weeks	Max dose of 120mg THC and 120mg CBD	DE-P2
Ware 2010b[20] (Canada)	Crossover RCT	Total N = 23 Age = 45.4 (12.3) Male % = 47.8	Analgesic and impact on mental health outcomes	Adjuvant	*Cannabis sativa* (smoked)	Placebo	Five days	1) 2.5% 2) 6% 3) 9.4%	DE-P2
Weber, 2010[21] (Switzerland)	Crossover RCT	Total N = 27 Age = 57 (12) Male % = 74.1	Analgesic, functional ability, quality of life, quality of sleep, antidepressant	NR	Dronabinol (oral)	Placebo	NR	5mg	DE-P2
Wilsey 2008[22] (USA)	Crossover RCT	Total N = 38		Adjuvant	*Cannabis sativa* (vaporised)	Placebo	One day	1) 3.5%	--

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Comparator	Treatment duration	Daily dose (lower and upper limits)	Outcomes included in quantitative synthesis[a]
		Age = NR Male % = 52.6	Analgesic and impact on mental health outcomes					2) 7%	
Zajicek 2003[23] (UK)	Crossover RCT	Total N = 630 Age = 50.55 (7.9) Male % = 33.65%	Antispasticity, analgesic, and impact on mental health outcomes	Adjuvant	1) Dronabinol (oral)	Placebo	14 weeks	NR (10-25mg)	DE-P2
					2) THC:CBD extract (oral)		14 weeks	NR (10-25mg THC and 5-12.5mg CBD)	
ANXIETY									
Abrams 2007[4] (USA)	Parallel RCT	Total N = 55 Age = 48.5 (6.5) Male % = 85.7	Analgesic and impact on mental health outcomes	Adjuvant	*Cannabis sativa* (smoked)	Placebo	Five days	3.56% THC	--
Aragona 2009[5] (Italy)	Crossover RCT	Total N = 17 Age = 49.8 (6.64) Male % = 35.3	Antispasticity and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	3 weeks	22.14mg THC and 20.5mg CBD	AN-P2
Bergamaschi 2011[24] (Brazil)	Parallel RCT	Total N = 36 Age = 23.6 (2.7) Male % = 50	Anxiolytic and quality of life	Primary	CBD extract (oral)	Placebo	One day	600mg	AN-P2
Crippa 2011[25] (Brazil)	Crossover RCT	Total N = 10 Age = 24.2 (3.7) Male % = 100	Anxiolytic and quality of life	Primary	CBD extract (oral)	Placebo	One day	400mg	AN-P2
DeVries 2017[26] (Netherlands)	Parallel RCT	Total N = 65 Age = 52.9 (9.65) Male % = 50	Analgesic, quality of life, change in functioning, and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	Placebo	50-52 days	NR (9-24mg)	--
Fabre 1981b[3] (USA)	Parallel RCT	Total N = 20 Age = 29 (NR) Male % = 75	Anxiolytic and global impression of change	Primary	Nabilone (oral)	Placebo	Four weeks	3mg	--
Frank 2008[9] (UK)	Crossover RCT	Total N = 96 Age = 50.15 (13.69) Male % = 52	Analgesic and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Active: dihydrocodeine	Six weeks	NR (0.25-2mg)	--
Malik 2017[10] (USA)	Parallel RCT	Total N = 19 Age = 43 (NR) Male % = 15.4	Analgesic and impact on mental health outcomes	NR	Dronabinol (oral)	Placebo	Four weeks	10mg	AN-P2
Moreno 2016[11] (Spain)	Crossover RCT	Total N = 25 Age = 47.6 (12.4) Male % = 56	Motor symptoms associated with Huntington's Disease, cognitive symptoms, mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Twelve weeks	NR (2.7-32.4mg THC and 2.5-30mg)	AN-P2
Muller-Vahl 2001[12] (Germany)	Crossover RCT	Total N = 12 Age = 34 (13) Male % = 91.7	Tic severity associated with Tourette's syndrome, quality of life, and impact on mental health outcomes	Adjuvant	THC extract (oral)	Placebo	One day	7.083mg (5-10mg)	AN-P2
Muller-Vahl 2003[27] (Germany)	Parallel RCT	Total N = 24 Age = 33 (11) Male % = 79.2	Tic severity and impact on mental health outcomes	Adjuvant	THC extract (oral)	Placebo	Six weeks	NR (2.5-10mg)	--
Narang 2008a[1] (USA)	Crossover RCT	Total N = 30 Age = 43.76 (11.8) Male % = 46.7	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	Placebo	One day	1) 10mg 2) 20mg	--
Pini 2012[15] (Italy)	Crossover RCT	Total N = 30 Age = 52.7 (9.6) Male % = 33.3	Analgesic and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Active: ibuprofen	Eight weeks	0.5mg	AN-P2
Rog 2005[17] (UK)	Parallel RCT	Total N = 66 Age = 49.2 (8.3) Male % = 21.2	Analgesic and impact on mental health outcomes	Adjuvant	Nabiximols (oromucosal spray)	Placebo	Four weeks	25.92mg THC (5.4-67.5mg) + 24mg CBD (5-62.5mg)	AN-P2
Skrabek 2008[28] (Canada)	Parallel RCT	Total N = 40 Age = 47.6 (9.13) Male % = 7	Analgesic, quality of life, and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Placebo	Four weeks	NR (0.5-2mg)	AN-P2
Toth 2012b[2] (Canada)	Parallel RCT	Total N = 26 Age = 61.2 (14.95) Male % = 53.8	Analgesic, quality of life, and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Placebo	Four weeks	2.24mg (1-4mg)	AN-P2
ADHD									
Cooper 2017[29] (UK)	Parallel RCT	Total N = 30 Age = 37.9 (11.6) Male % = 63.3	ADHD symptoms, impairments in cognition, and impairments in emotional lability	Primary	Nabiximols (oromucosal spray)	Placebo	Six weeks	12.69mg THC (2.7-35.1mg) and 11.75mg CBD (2.5-32.5mg)	AD-P1 AD-S1 AD-S2 AD-S3
TIC /TOURETTE'S DISORDER									
Muller-Vahl 2001[12] (Germany)	Crossover RCT	Total N = 12 Age = 34 (13) Male % = 91.7	Tic severity associated with Tourette's syndrome, quality of life, and impact on mental health outcomes	Adjuvant	THC extract (oral)	Placebo	One day	7.083mg (5-10mg)	TT-P1
Muller-Vahl 2003[27] (Germany)	Parallel RCT	Total N = 24 Age = 33 (11) Male % = 79.2	Tic severity and impact on mental health outcomes	Adjuvant	THC extract (oral)	Placebo	Six weeks	NR (2.5-10mg)	TT-P1

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Comparator	Treatment duration	Daily dose (lower and upper limits)	Outcomes included in quantitative synthesis[a]
PTSD									
Jetly 2015[30] (Canada)	Crossover RCT	Total N = 10 Age = 43.6 (8.2) Male % = 100	PTSD symptoms, nightmares, quality of life, and global impression of change	Adjuvant	Nabilone (oral)	Placebo	Seven weeks	1.95mg (0.5-3mg)	PT-S1 PT-S4 PT-S5
PSYCHOSIS									
Bhattacharyya 2018[31] **(UK)**	Parallel RCT	Total N = 52 Age = 23.9 (4.8) Male % = 53.8	Antipsychotic	Primary	CBD extract (oral)	Placebo	Three weeks	600mg	--
Boggs 2018[32] **(USA)**	Parallel RCT	Total N = 36 Age = 47.4 (9.4) Male % = 69.4	Antipsychotic and cognitive enhancer	Adjuvant	CBD extract (oral)	Placebo	Six weeks	600mg	PS-P2 PS-S2
D'Souza 2005[33] **(USA)**	Crossover RCT	Total N = 35 Age = 34.7 (11.2) Male % = 68.6	Antipsychotic and cognitive enhancement	Adjuvant	THC extract (intravenous)	Placebo	Three days	2.5mg 5mg	--
Hallak 2010[34] **(Brazil)**	Parallel RCT	Total N = 28 Age = NR Male % = 64.3	Cognitive enhancer and fear responses	Adjuvant	CBD extract (oral)	Placebo	One day	300mg 600mg	PS-S2
Leweke 2012[35] **(USA)**	Parallel RCT	Total N = 42 Age = 30.1 (8.9) Male % = 82.1	Antipsychotic, anxiolytic, and impact on anandamide signalling	Adjuvant	CBD extract (oral)	Active: Amisulpride	Four weeks	800mg	PS-P2
McGuire 2018[36] **(Multicentre—UK, Romania, and Poland)**	Parallel RCT	Total N = 88 Age = 40.8 (11.7) Male % = 58	Antipsychotic, cognitive enhancer, impression of change, physical functioning, and quality of life	Adjuvant	CBD extract (oral)	Placebo	Six weeks	1000mg	PS-P2 PS-S1 PS-S2

Note: ITT = intention to treat; LOCF = last observation carried forward; NR = not reported. IBD = inflammatory bowel disease

a. DE-P1- Remission – absence of a depressive disorder diagnosis using validated scales; DE-P2 - Change in depressive symptoms using self-report scales or items; DE-S1 - Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment; AN-P1 - Remission – the absence of an anxiety disorder diagnosis using validated scales; AN-P2 - Change in anxiety symptoms using self-report scales or items; AN-S1 - Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment; AD-P1 - Change in ADHD symptom-related behaviour using standardised measures – any context; AD-P2 - Change in ADHD symptom-related behaviour in the home using standardised measures; AD-P3 - Change in ADHD symptom-related behaviour in school using standardised measures; AD-S1 - Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment; AD-S2 - Change in cardiovascular effects; AD-S3 - Weight changes; TT-P1 - Change in Tic severity measured using standardised measures; TT-S1 - Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment; TT-S2 - Change in cardiovascular effects; TT-S3 - Weight changes; PT-P1 - Change in baseline to endpoint of PTSD symptom severity using valid and reliable clinician-rated scales; PT-P2 - Change in severity of self-reported traumatic stress symptoms using self-report scales or items; PT-S1 - Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment; PT-S2 - Change in severity of depressive symptoms using a standardised measure; PT-S3 - Change in severity of anxiety symptoms using a standardised measure; PT-S4 - Change in sleep quality; PT-S5 - Change in frequency of nightmares; PS-P1 - Whether patients still meet criteria for a diagnosis post-treatment; PS-P2 - Change in positive and negative symptoms of psychosis; PS-S1 - Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment; PS-S2 - Change in cognitive functioning; PS-S3 - Measures of emotional functioning – including depression, anxiety, mood, and social skills; ALL-S1a - Adverse events (AEs) - all-cause; ALL-S1b - Serious adverse events (SAEs; as defined by authors) - all-cause; ALL-S1c - Treatment-related adverse events (TAEs) - all-cause; ALL-S2a - Study withdrawals - all-cause; ALL-S2b - Study withdrawals - due to AEs

Table E3: Characteristics of included observational studies of cannabis and cannabinoids for the treatment of mental health

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
Depression							
Attal 2004[37] (France)	Open label	Total N = 8 Age = 63.3 (14) Male % = 50	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	16 weeks	16.6mg (7.5-25mg)
Bahorik 2017[38] (USA)	Retrospective cohort	Total N = 307 Age = 37.2 (12.9) Male % = 29.6	Antidepressant, anxiolytic and quality of life	NR	Marijuana (unclear)	12-26 weeks	NR
Bellnier 2017[39] (NR)	Chart review	Total N = 36 Age = 71 (7) Male % = 25	Anxiolytic, antidepressant, quality of life and analgesic	NR	Marijuana (unclear)	NR	NR
Bestard 2011[40] (Canada)	Open label	Total N = 249 Age = 61.2 (11.3) Male % = 40.9	Analgesic and impact on mental health outcomes	1) Adjuvant	Nabilone (oral)	Six months	3.02mg
				2) Primary	Nabilone (oral)	Six months	3.05mg
Blaas 2008[41] (Austria)	Case series	Total N = 1 Age = 48 Male % = 0	Antidepressant and quality of life	Adjuvant	Dronabinol (oral)	312 weeks	NR (5-10mg)
		Total N = 1 Age = 22 Male % = 0	Antidepressant and quality of life	Primary	Dronabinol (oral)	52 weeks	10mg (2.5-10mg)
Clermont-Gnamien 2002[42] (France)	Prospective cohort	Total N = 7 Age = 60 (14) Male % = 57.1	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	55.4 days	15mg (5-25mg)
Gerardi 2016[43] (Italy)	Open label	Total N = 15 Age = NR Male % = 13.3	Analgesic, fatigue, sleep disturbances, and antidepressant	Adjuvant	*Cannabis Sativa* (oral)	Two months	NR (60-120mg)
Gruber 1996[44] (USA)	Case series	Total N = 1 Age = 20 Male % = 100	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
		Total N = 1 Age = 16 Male % = 100	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
		Total N = 1 Age = 27	Antidepressant	Adjuvant	*Cannabis sativa* (smoked)	NR	NR

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
		Male % = 0					
		Total N = 1 Age = 23 Male % = 0	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
		Total N = 1 Age = 28 Male % = 100	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
Hagenbach 2007[45] (Switzerland)	Open label	Total N = 25 Age = 42.6 (NR) Male % = 92	Anti-spasticity, analgesic, and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	Six weeks	31mg (15-60mg)
Haroutiunian 2008[46] (Israel)	Open label	Total N = 13 Age = 46 (17) Male % = 53.8	Analgesic and impact on mental health outcomes	Adjuvant	THC extract (oral)	35.1 weeks	NR (10-15mg)
Johnson 2016[47] (USA)	Retrospective cohort	Total N = 700 Age = 47.1 (15) Male % = 91	PTSD symptoms, antidepressant, and suicidal ideation	NR	*Cannabis sativa* (unclear)	NR	NR
Lahat 2012[48] (Israel)	Open label	Total N = 13 Age = 41.8 (10.2) Male % = 69.2	IBD symptoms management, appetite stimulation/weight gain, quality of life, and impact on mental health outcomes	Adjuvant	*Cannabis sativa* (smoked)	12 weeks	~1.8g
Martinez-Rodriguez 2008[49] (Spain)	Cross-sectional study	Total N = 175 Age = 42.84 (11.23) Male % = 35.5	Analgesic, anti-spasticity, and impact on mental health outcomes	NR	*Cannabis sativa* (smoked, ingested)	NR	NR
Maurer 1990[50] (Switzerland)	Case study	Total N = 1 Age = 28 (NR) Male % = 100	Anti-spasticity, analgesic, and impact on mental health outcomes	Adjuvant	THC extract (oral)	Five months	NR
Narang 2008b[1] (USA)	Open label	Total N = 28 Age = 43.76 (11.8) Male % = 46.7	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	Four weeks	NR (5-60mg)
Neff 2002[51] (USA)	Case series	Total N = 1 Age = 22 Male % = 0	Pruritis, quality of life, and impact on mental health outcomes	NR	Dronabinol (oral)	Two months	5mg
		Total N = 1 Age = 31 Male % = 0	Pruritis, quality of life, and impact on mental health outcomes	NR	Dronabinol (oral)	NR	5mg
		Total N = 1	Pruritis, quality of life, and impact	NR	Dronabinol (oral)	NR	2.5mg

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
		Age = 57 Male % = 0	on mental health outcomes				
Rudich 2003[52] (Canada)	Case report	Total N = 2 Age = NR Male % = 50	Academic performance, mood and sleep	NR	Dronabinol (oral)	NR	NR (5-25mg)
Shah 2017[53] (USA)	Retrospective cohort	Total N = 48 Age = 45.1 (14.02) Male % = 41.67	Analgesic and impact on mental health outcomes	Adjuvant	Unknown (smoked or oral)	NR	NR
Toth 2012a[2] (Canada)	Prospective cohort	Total N = 37 Age = 62.2 (9.3) Male % = 45	Analgesic, quality of life, and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Four weeks	2.24mg (1-4mg)
Ware 2015[54] (Canada)	Prospective cohort	Total N = 431 Age = 48.95 (NR) Male % = 43.1	Analgesic and impact on mental health outcomes	Adjuvant	*Cannabis sativa* (smoked, oral, vaporised)	52 weeks	2.46g (0.09-13.4g)
Weber 2009[55] (Germany)	Retrospective survey	Total N = 124 Age = 55(13) Male % = 37.9	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	31 weeks	7.5mg
Anxiety							
Attal 2004[37] (France)	Open label	Total N = 8 Age = 63.3 (14) Male % = 50	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	16 weeks	16.6mg (7.5-25mg)
Bahorik 2017[38] (USA)	Retrospective cohort	Total N = 307 Age = 37.2 (12.9) Male % = 29.6	Antidepressant, anxiolytic and quality of life	NR	Marijuana (unclear)	12-26 weeks	NR
Bellnier 2017[39] (NR)	Chart review	Total N = 36 Age = 71 (7) Male % = 25	Anxiolytic, antidepressant, quality of life and analgesic	NR	Marijuana (unclear)	NR	NR
Bestard 2011[40] (Canada)	Open label	Total N = 249 Age = 61.2 (11.3) Male % = 40.9	Analgesic and impact on mental health outcomes	1) Adjuvant	Nabilone (oral)	Six months	3.02mg
				2) Primary	Nabilone (oral)	Six months	3.05mg
Clermont-Gnamien 2002[42] (France)	Prospective cohort	Total N = 7 Age = 60 (14) Male % = 57.1	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	55.4 days	15mg (5-25mg)
Deutsch 2008[56] (NR)	Case study	Total N = 1 Age = 52 Male % = 0	Antidepressant, anxiolytic and mood	NR	Dronabinol (oral)	NR	2.5mg (2.5-5mg)

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
Fabre 1981a[3] (USA)	Open label	Total N = 5 Age = 29.4 (NR) Male % = 100	Anxiolytic and global impression of change	Primary	Nabilone (oral)	Four weeks	2.8mg (2-8mg)
Gerardi 2016[43] (Italy)	Open label	Total N = 15 Age = NR Male % = 13.3	Analgesic, fatigue, sleep disturbances, and antidepressant	Adjuvant	*Cannabis Sativa* (oral)	Two months	NR (60-120mg)
Glass 1981[57] (USA)	Prospective cohort	Total N = 9 Age = 25.4 (NR) Male % = 44.4	Anxiolytic	NR	Nabilone (unclear)	One day	NR (0.5-5mg)
Gruber 1996[44] (USA)	Case series	Total N = 1 Age = 20 Male % = 100	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
		Total N = 1 Age = 16 Male % = 100	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
		Total N = 1 Age = 27 Male % = 0	Antidepressant	Adjuvant	*Cannabis sativa* (smoked)	NR	NR
		Total N = 1 Age = 23 Male % = 0	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
		Total N = 1 Age = 28 Male % = 100	Antidepressant	Adjuvant	*Cannabis sativa* (unclear)	NR	NR
Leehey 2017[58] (USA)	Open label	Total N = 6 Age = 69.8 (4.7) Male % = 83.3	Parkinson's Disease symptoms, analgesic, quality of life, and impact on mental health outcomes	NR	CBD extract (unclear)	27 days	NR (5-25mg)
Martinez-Rodriguez 2008[49] (Spain)	Cross-sectional study	Total N = 175 Age = 42.84 (11.23) Male % = 35.5	Analgesic, anti-spasticity, and impact on mental health outcomes	NR	*Cannabis sativa* (smoked, ingested)	NR	NR
Passie 2012[59] (Unclear)	Case study	Total N = 1 Age = 19 (NR) Male % = 100	PTSD symptoms and impact on mental health outcomes	Adjuvant	Cannabis Resin (smoking)	NR	NR
Shannon 2016[60] (USA)	Case study	Total N = 1 Age = 10 (NR) Male % = 0	PTSD symptoms, anxiolytic, and quality of life	Adjuvant	CBD extract (oral)	20 weeks	NR (6-25mg)

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
Toth 2012a[2] (Canada)	Prospective cohort	Total N = 37 Age = 62.2 (9.3) Male % = 45	Analgesic, quality of life, and impact on mental health outcomes	Adjuvant	Nabilone (oral)	Four weeks	2.24mg (1-4mg)
Weber 2009[55] (Germany)	Retrospective survey	Total N = 124 Age = 55(13) Male % = 37.9	Analgesic and impact on mental health outcomes	Adjuvant	Dronabinol (oral)	31 weeks	7.5mg
ADHD							
Hasan 2010[61] (Germany)	Case study	Total N = 1 Age = 15 (NR) Male % = 100	ADHD symptoms, tic severity, and quality of life	Adjuvant	THC extract (unclear)	Nine weeks	NR (5-15mg)
Muller-Vahl 1998[62] (Germany)	Retrospective survey	Total N = 17 Age = 30.5 (NR) Male % = 88.2	ADHD symptoms, tic severity, and obsessive-compulsive symptoms	Adjuvant	*Cannabis sativa* (smoked)	NR	NR
Tic/Tourette's disorder							
Arad 2017[63] (Israel)	Retrospective survey	Total N = 24 Age = 35.1 (12.5) Male % = 75	Tic severity, premonitory urges, muscular pain, and quality of life	NR	*Cannabis sativa* (smoked)	15.2 weeks	27.9grams (monthly average)
Deutsch 2008[56] (NR)	Case study	Total N = 1 Age = 52 Male % = 0	Tic severity and anti-spasticity	NR	Dronabinol (unclear)	NR	NR (5-10mg)
Hasan 2010[61] (Germany)	Case study	Total N = 1 Age = 15 (NR) Male % = 100	ADHD symptoms, tic severity, and quality of life	Adjuvant	THC extract (unclear)	Nine weeks	NR (5-15mg)
Hemming 1993[64] (Australia)	Case study	Total N = 1 Age = 36 Male % = 100	Tic severity	Primary	*Cannabis sativa* (smoked)	52 weeks	NR
Muller-Vahl 1998[62] (Germany)	Retrospective survey	Total N = 17 Age = 30.5 (NR) Male % = 88.2	ADHD symptoms, tic severity, and obsessive-compulsive symptoms	Adjuvant	*Cannabis sativa* (smoked)	NR	NR
Muller-Vahl 2002[65] (Germany)	Case study	Total N = 1 Age = 24 Male % = 0	Tic severity and premonitory urges	Adjuvant	THC extract (oral)	24 weeks	10mg
PTSD							
Cameron 2014[66] (Canada)	Chart review	Total N = 104 Age = 32.7 (NR)	PTSD symptoms, anxiolytic, antidepressant, analgesic, and	NR	Nabilone (oral)	11.2 weeks	4mg (0.5-6mg)

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
		Male % = 100	quality of life				
Fraser 2009[67] (NR)	Chart review	Total N = 47 Age = 44 (9) Male % = 43	PTSD symptoms, nightmares, and quality of life	Adjuvant	Nabilone (oral)	16-52 weeks	0.5mg (0.2-4mg)
Greer 2014[68] (USA)	Chart review	Total N = 80 Age = NR Male % = NR	PTSD symptoms	NR	*Cannabis sativa* (unclear)	NR	NR
Johnson 2016[47] (USA)	Retrospective cohort	Total N = 700 Age = 47.1 (15) Male % = 91	PTSD symptoms, antidepressant, and suicidal ideation	NR	*Cannabis sativa* (unclear)	NR	NR
Mashiah 2012[69] (Israel)	Open label	Total N = 29 Age = NR Male % = 100	PTSD symptoms and quality of life	Adjuvant	THC:CBD extract (smoked)	~52 weeks	100mg per month
Passie 2012[59] (Unclear)	Case study	Total N = 1 Age = 19 (NR) Male % = 100	PTSD symptoms and impact on mental health outcomes	Adjuvant	Cannabis Resin (smoking)	NR	NR
Quinn 2016[70] (USA)	Case study	Total N = 1 Age = 39 (NR) Male % = 100	PTSD symptoms and anxiolytic	NR	*Cannabis sativa* (unclear)	~26 weeks	NR
Reznik 2012[71] (Israel)	Prospective cohort	Total N = 167 Age = NR Male % = NR	PTSD symptoms, impression of change, and quality of life	Adjuvant	*Cannabis sativa* (unclear)	156 weeks	NR (2-3g)
Roitman 2014[72] (Israel)	Open label	Total N = 10 Age = 52.3 (8.3) Male % = 70	PTSD symptoms, nightmares, and quality of life	Adjuvant	THC extract (oral)	Three weeks	10mg (5-10mg)
Shannon 2016[60] (USA)	Case study	Total N = 1 Age = 10 (NR) Male % = 0	PTSD symptoms, anxiolytic, and quality of life	Adjuvant	CBD extract (oral)	20 weeks	NR (6-25mg)
Wilkinson 2015[73] (USA)	Prospective cohort	Total N = 2276 Age = 51.7 (8.6) Male % = 96.7	PTSD symptoms	Adjuvant	*Cannabis sativa* (unclear)	16 weeks	NR
Psychosis							
Goswami 2004[74] (India)	Cross-sectional study	Total N = 22 Age = 33.5 (9.4) Male % = 100	Antipsychotic, antidepressant, anxiolytic, and quality of life	Adjuvant	*Cannabis sativa* (unclear)	NR	NR

Study ID (Country)	Type of study	Sample N Mean age (SD) Male %	Indication(s)	Place in therapeutic hierarchy	Cannabinoid classification	Treatment duration	Daily dose (lower and upper limits)
Kolliakou 2015[75] (UK)	Prospective cohort	Total N = 321 Age = NR Male % = 75	Enhancement (e.g. "makes you feel good"), social motives, coping with unpleasant affect, conformity and acceptance, and relief of positive symptoms and side effects	NR	*Cannabis sativa* (unclear)	13-26 weeks	NR
Mane 2015[76] (Spain)	Retrospective survey	Total N = 119 Age = 24.4 (3.9) Male % = 66.7	Antipsychotic, antidepressant, and quality of life	NR	*Cannabis sativa* (smoked)	NR	NR
Zuardi 2006[77] (Brazil)	Case series	Total N = 1 Age = 23 Male % = 100	Antipsychotic and impression of change	Primary	CBD extract (unclear)	Four weeks	NR (40-1280mg)
		Total N = 1 Age = 23 Male % = 100	Antipsychotic and impression of change	Primary	CBD extract (unclear)	Four weeks	NR (40-1280mg)
		Total N = 1 Age = 22 Male % = 100	Antipsychotic and impression of change	Primary	CBD extract (unclear)	Four weeks	NR (40-1280mg)
Zuardi 2009[78] (Brazil)	Open label	Total N = 6 Age = 58.8 (14.9) Male % = 66.7	Antipsychotic, Parkinson's Disease symptoms, impression of change, and quality of life	Adjuvant	CBD extract (oral)	Four weeks	NR (150-400mg)

Appendix F: Forest plots for primary outcomes, adverse events, and withdrawals due to adverse events

Figure F1: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of depressive symptoms

Study or Subgroup	Std. Mean Difference	SE	Cannabis Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 THC vs. Active						
Pini 2012	0	0.088	26	26	10.5%	0.00 [-0.17, 0.17]
Subtotal (95% CI)			**26**	**26**	**10.5%**	**0.00 [-0.17, 0.17]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.2.2 THC vs. Placebo						
Aragona 2009	-0.0472	0.109	17	17	9.4%	-0.05 [-0.26, 0.17]
Ball 2015	0.16363	0.15239	238	118	7.4%	0.16 [-0.14, 0.46]
Fairhurst 20xx	-0.1734	0.248	47	25	4.2%	-0.17 [-0.66, 0.31]
Malik 2017	0.6394	0.5763	7	6	1.1%	0.64 [-0.49, 1.77]
Moreno 2012	-0.4115	0.093	25	25	10.2%	-0.41 [-0.59, -0.23]
Muller-Vahl 2001	-0.0235	0.129	12	12	8.4%	-0.02 [-0.28, 0.23]
Portenoy 2012	0.2581	0.1493	90	91	7.5%	0.26 [-0.03, 0.55]
Rog 2005	0.0627	0.2482	33	32	4.2%	0.06 [-0.42, 0.55]
Toth 2012b	-0.0745	0.3924	13	13	2.1%	-0.07 [-0.84, 0.69]
Wade 2004	0.1212	0.1608	78	77	7.0%	0.12 [-0.19, 0.44]
Weber 2010	0.036	0.089	25	25	10.4%	0.04 [-0.14, 0.21]
Zajicek 2003	-0.47955	0.14935	417	213	7.5%	-0.48 [-0.77, -0.19]
Subtotal (95% CI)			**1002**	**654**	**79.5%**	**-0.05 [-0.20, 0.11]**
Heterogeneity: Tau² = 0.04; Chi² = 33.12, df = 11 (P = 0.0005); I² = 67%						
Test for overall effect: Z = 0.59 (P = 0.56)						
1.2.3 Plant vs. Placebo						
Ware 2010b	-0.141	0.098	21	21	10.0%	-0.14 [-0.33, 0.05]
Subtotal (95% CI)			**21**	**21**	**10.0%**	**-0.14 [-0.33, 0.05]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)			**1049**	**701**	**100.0%**	**-0.05 [-0.18, 0.07]**
Heterogeneity: Tau² = 0.03; Chi² = 34.31, df = 13 (P = 0.001); I² = 62%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Chi² = 1.17, df = 2 (P = 0.56), I² = 0%						

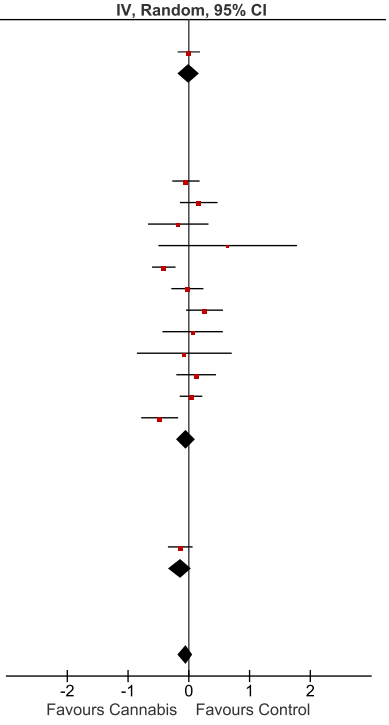


Figure F2: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of anxiety symptoms

Study or Subgroup	Std. Mean Difference	SE	Cannabis Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 CBD vs. Placebo						
Bergamaschi 2011	-0.2275	0.4098	12	12	6.2%	-0.23 [-1.03, 0.58]
Crippa 2011	-1.3966	0.199	10	10	11.2%	-1.40 [-1.79, -1.01]
Subtotal (95% CI)			**22**	**22**	**17.4%**	**-0.87 [-2.01, 0.27]**
Heterogeneity: Tau² = 0.58; Chi² = 6.59, df = 1 (P = 0.01); I² = 85%						
Test for overall effect: Z = 1.49 (P = 0.14)						
2.5.2 THC vs. Active						
Pini 2012	-0.1233	0.088	26	26	14.0%	-0.12 [-0.30, 0.05]
Subtotal (95% CI)			**26**	**26**	**14.0%**	**-0.12 [-0.30, 0.05]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
2.5.3 THC vs. Placebo						
Aragona 2009	-0.1538	0.109	17	17	13.6%	-0.15 [-0.37, 0.06]
Malik 2017	0.326	0.5616	7	6	4.1%	0.33 [-0.77, 1.43]
Moreno 2012	-0.4115	0.093	25	25	13.9%	-0.41 [-0.59, -0.23]
Muller-Vahl 2001	0.1243	0.13	12	12	13.1%	0.12 [-0.13, 0.38]
Rog 2005	-0.28	0.249	33	32	9.8%	-0.28 [-0.77, 0.21]
Skrabek 2008	-0.8	0.33	20	20	7.8%	-0.80 [-1.45, -0.15]
Toth 2012b	-0.73	0.407	13	13	6.3%	-0.73 [-1.53, 0.07]
Subtotal (95% CI)			**127**	**125**	**68.6%**	**-0.25 [-0.49, -0.01]**
Heterogeneity: Tau² = 0.05; Chi² = 17.24, df = 6 (P = 0.008); I² = 65%						
Test for overall effect: Z = 2.07 (P = 0.04)						
Total (95% CI)			**175**	**173**	**100.0%**	**-0.37 [-0.63, -0.11]**
Heterogeneity: Tau² = 0.12; Chi² = 52.47, df = 9 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 2.78 (P = 0.005)						
Test for subgroup differences: Chi² = 2.15, df = 2 (P = 0.34), I² = 7.0%						

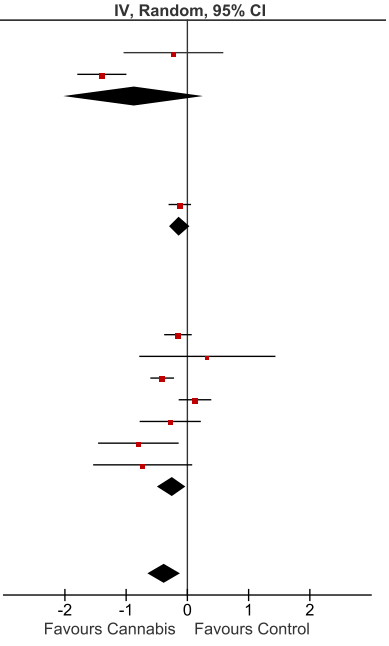


Figure F3: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of ADHD symptoms

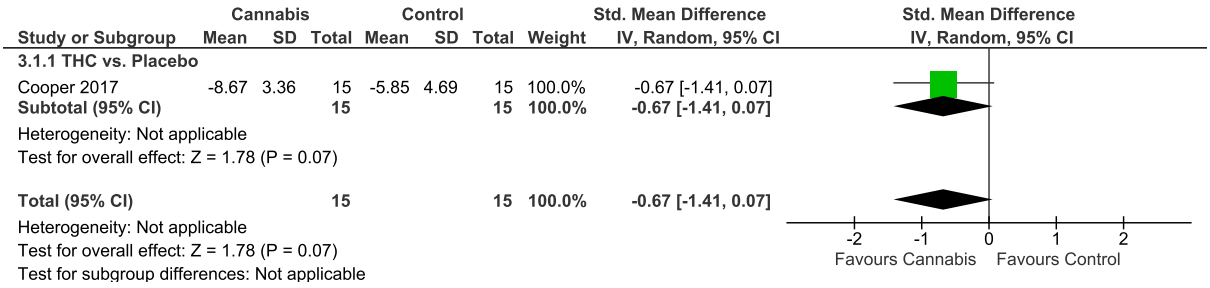


Figure F4: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of Tic/Tourette's symptoms

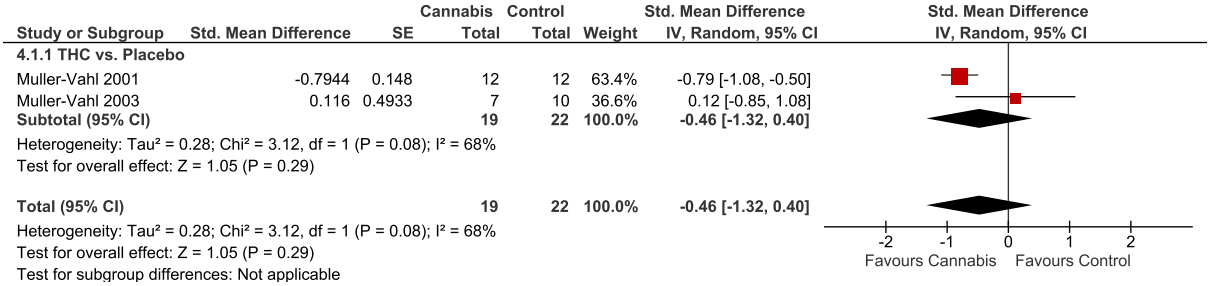


Figure F5: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of psychosis upon total symptoms of psychosis

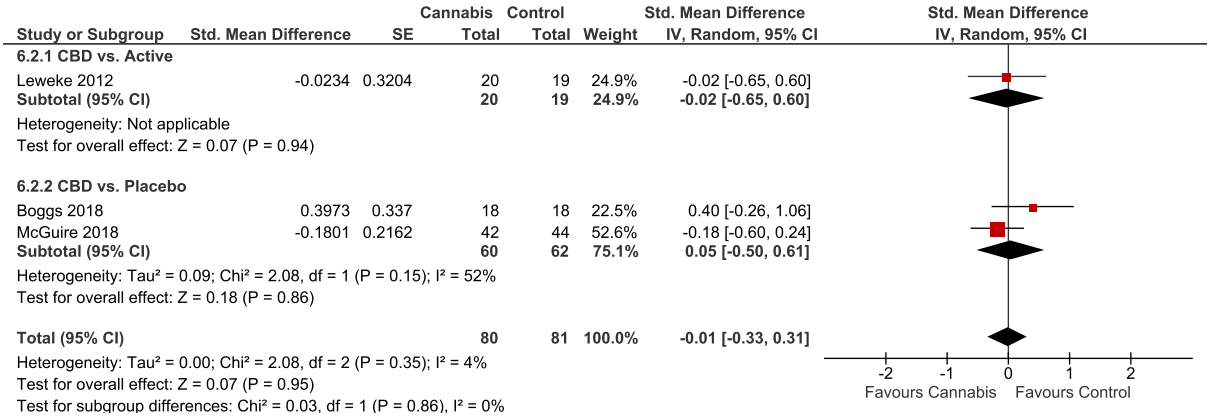


Figure F6: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of psychosis upon positive symptoms of psychosis

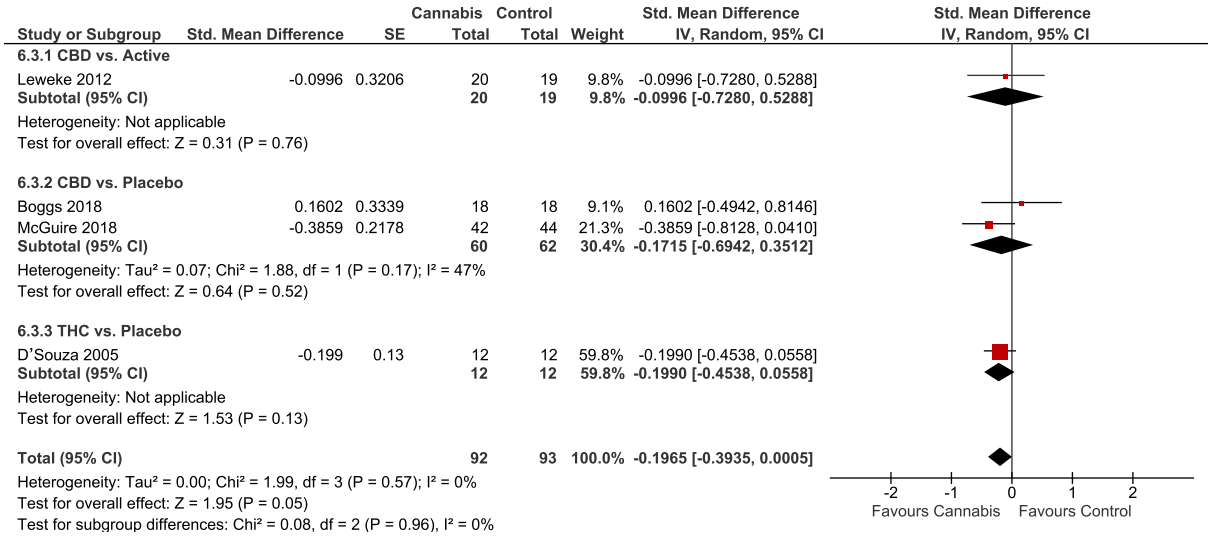


Figure F7: Forest plot for RCT study evidence for impact of cannabis or cannabinoids used for treatment of psychosis upon negative symptoms of psychosis

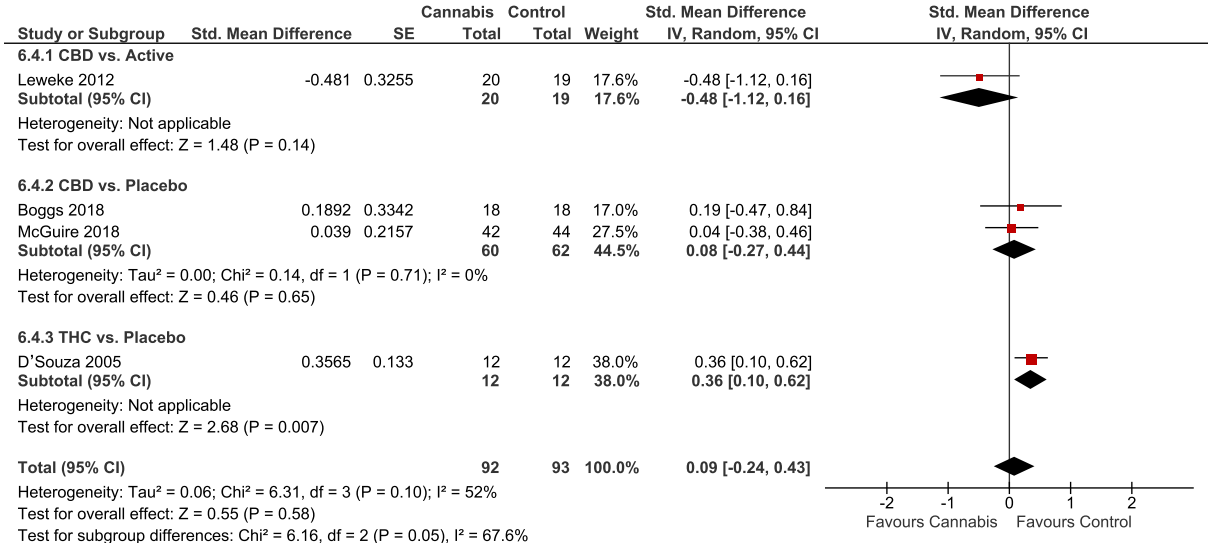


Figure F8: Forest plot for RCT study evidence for impact of cannabis or cannabinoids on adverse events

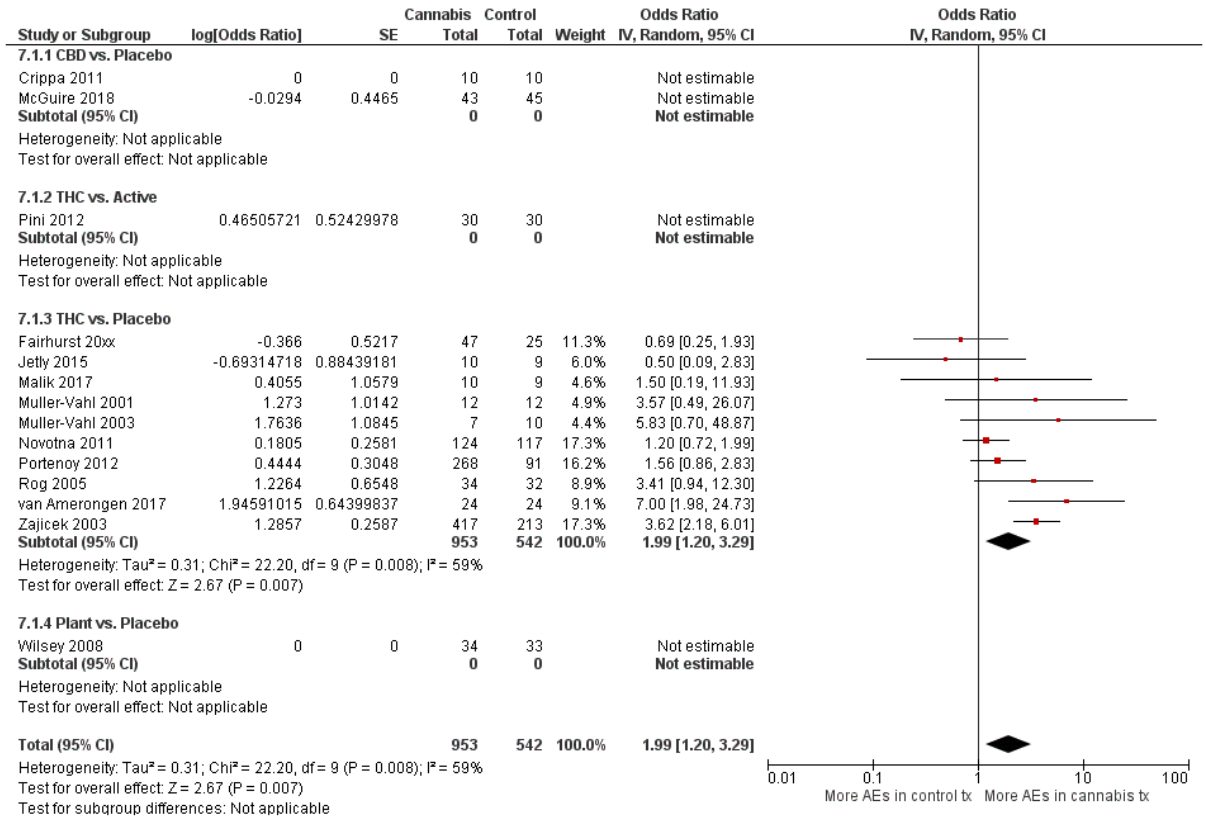
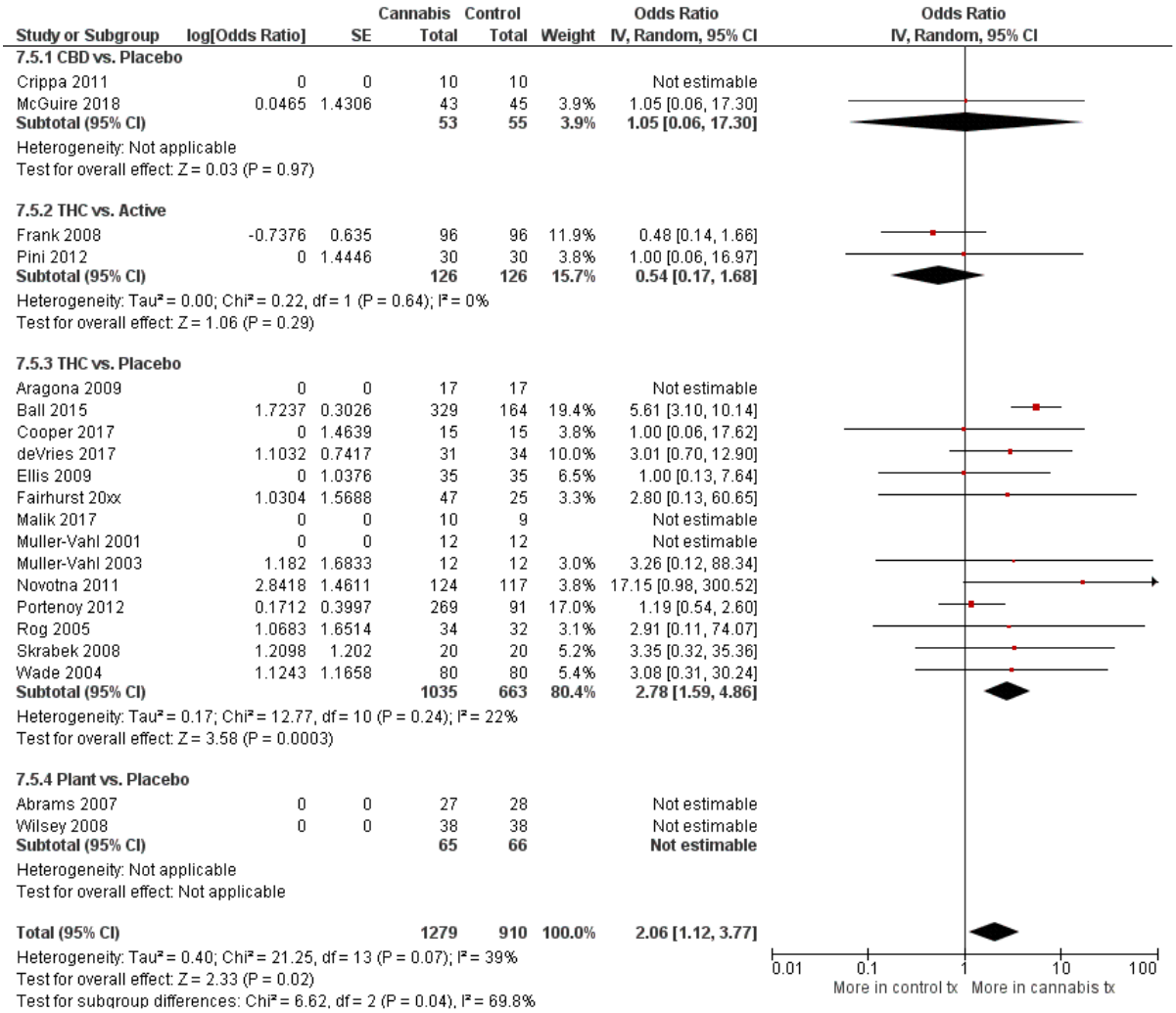


Figure F9: Forest plot for RCT study evidence for impact of cannabis or cannabinoids on withdrawals due to adverse events



Appendix G: Further details on the data analytic approach

All analyses were conducted using Review Manager (RevMan) version 5.3[79]. Meta-analyses included parallel and cross-over RCTs, which were combined using random-effects, generic inverse variance meta-analyses. Random-effects models assume that variability in the effect estimates occurs due to both variability in the true treatment effects and sampling error, whereas fixed-effects models assume that variability in the effect estimates occurs due to sampling error alone. Hence, in our study, the random-effects model better accounts for the fact that the true effectiveness of cannabinoids might vary from study to study due to such factors as varying doses, lengths of treatments, or population characteristics. Heterogeneity was assessed using the I^2 statistic. I^2 values of 0-39%, 40-74%, and 75-100% can be considered unimportant, moderate/substantial, and high levels of inconsistency across studies, respectively[80].

Continuous and dichotomous outcomes were pooled as standardised mean differences (SMD) and odds ratios (ORs), respectively. A common rule of thumb for interpreting SMDs is: 0.2, 0.5, and 0.8 represent small, medium, and large effects, respectively[81]. Where data were available, change from baseline scores were used to calculate effect sizes, with baseline standard deviations (SDs) substituted when change SDs were missing. Post-treatment scores were used to calculate effect sizes when change from baseline scores were missing. Studies that did not report the outcomes in enough detail to permit full data extraction were not included in the quantitative synthesis.

We used the following methods to manage variations in study design and avoid unit-of-analysis errors. The SMDs and corresponding standard errors (SEs) for continuous outcomes from cross-over trials were calculated as per Cochrane recommendations[82], with the correlation coefficient estimated as 0.9, based on past literature. This means that a participant's responses to the cannabinoid and comparator treatments are assumed to correlate at 0.9. The ORs for dichotomous outcomes from cross-over trials were calculated using the marginal Becker-Balagtas method[83,84], with the correlation coefficient arbitrarily estimated as 0.5 when only the row/column totals were available. In the minority of instances where multiple eligible treatment groups per trial were reported we combined these into a single group (two studies for depression outcomes[20,23] and four for adverse events and withdrawals[1,16,22,23]). In one case where data were not available to combine treatment groups, we included the most intensive treatment group only. Where multiple measures of a single outcome were reported we selected the measure most consistent across studies or most specific to the outcome (e.g., for depression, we selected measures of depression over measures of mental health more broadly). Where outcome data for multiple time points were reported we included the longest follow-up in all instances except one[6], where the longest follow-up (three years) was much longer than that in all other studies included (one day-20 weeks).

Table G1: Summary of the statistics and metrics used in this review

Statistic or metric	Definition	Some guiding notes on interpretation
Odds ratio (OR)	Ratio of the odds of an outcome with the active treatment to the odds of an outcome with placebo	The odds ratio represents the odds that a particular outcome will occur following a certain exposure, (e.g. medication) compared to the odds that the outcome will occur in the absence of the exposure. In short: ▪ OR = 1 Exposure to intervention does not change the odds of the outcome of interest. ▪ OR <1 Exposure to intervention is associated with lower odds of the outcome of interest. ▪ OR >1 Exposure to intervention is associated with increased odds of the outcome of interest.
Standardised mean difference (SMD)	Used when outcomes are continuous and measured using different instruments and thus combining raw means (via a mean difference) would not be meaningful; compares treatment and placebo group scores in each study relative to the variability observed in that study.	Interpretation of SMDs can sometimes be difficult as the outcome is expressed as units of standard deviation rather than units of a specific measurement scale, such as a 100mm visual analogue scale. A common rule of thumb for interpreting SMDs is: 0.2 represents a "small" effect, 0.5 represents a "moderate" effect and 0.8 represents a "large" effect[81].
Number needed to harm (NNH)	Number of people needed to treat for one additional person to experience the negative outcome of interest	The lower the NNH, the more harmful the intervention or exposure. A NNH of 1 means that, on average, every person exposed to an intervention will experience a negative outcome of interest.

Appendix H: Summary of evidence from randomised controlled trials on the use of medicinal cannabis for the treatment of mental health

Table H1: Summary of evidence from randomised controlled trials on the use of medicinal cannabis for the treatment of mental health

Disorder	Outcome	Comparator	Studies (participants)	Risk of Bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pooled SMD [95% CI]	I^2	Favours	GRADE
Depression	Remission from disorder	--	0 (0)	--	--	--	--	--	--	--	--	--
	Change in depressive symptoms†	Placebo	1 (42)	Not serious	Very serious	Serious	Serious	Likely	-0.14 [-0.33, 0.05]	NA	Neither	Very low
	Change in global functioning	--	0 (0)	--	--	--	--	--	--	--	--	--
Anxiety	--	--	0 (0)	--	--	--	--	--	--	--	--	--
ADHD	--	--	0 (0)	--	--	--	--	--	--	--	--	--
Tic/Tourette syndrome	--	--	0 (0)	--	--	--	--	--	--	--	--	--
PTSD	--	--	0 (0)	--	--	--	--	--	--	--	--	--
Psychosis	--	--	0 (0)	--	--	--	--	--	--	--	--	--

Note: † indicates outcomes for which forest plots are available on pp. 46-50. White cells are primary outcomes and shaded cells are secondary outcomes. NA = not applicable. In all comparisons the control group (placebo/active) is the reference group.

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