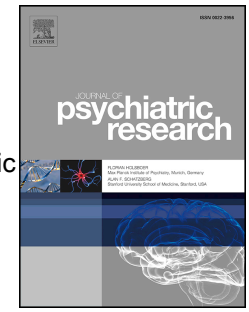

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Anees Bahji, Arthi Chinna Meyyappan, Emily R. Hawken

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Efficacy and acceptability of cannabinoids for anxiety disorders in adults: a systematic review & meta-analysis

Anees Bahji[1],* Arthi Chinna Meyyappan[1],* Emily R Hawken[1,2]

1. Department of Psychiatry, Queen's University, Kingston, Ontario, Canada
2. Providence Care Hospital, Kingston, Ontario, Canada

*Both authors contributed equally

Correspondence
Emily Hawken, MSc, PhD
Department of Psychiatry, Queen's University
Providence Care Hospital
752 King Street West, Kingston, ON, Canada K7L 4X3
Email: hawken@queensu.ca

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Objective: The aim of this study was to assess the efficacy and acceptability of cannabinoids for the treatment of anxiety disorders.

Methods: For this systematic review and meta-analysis, we searched for randomized trials utilizing cannabinoids for the treatment of adults with anxiety disorders. Primary outcomes were reduction in anxiety disorder symptoms, and study discontinuation due to adverse events. Evidence was synthesized as rate ratios (RRs) and as standardized mean differences (SMDs) using random-effects meta-analyses.

Results: A total of 14 eligible trials representing 1548 individuals (median age: 33 years; range: 28-44; 66% male) were identified. Cannabinoids reduced anxiety symptoms (SMD = -1.85, 95% CI: -2.61 to -1.09) without causing significant adverse events. Greater efficacy was observed among younger patients ($p<0.01$) and with longer treatment ($p<0.01$). However, publication bias was substantial, and after correction, the overall anxiolytic effect was not statistically significant.

Conclusions: While cannabinoids may be of potential value in the treatment of anxiety disorders, the routine use of these treatments is not supported by the available evidence after correction for publication bias.

Highlights

- Cannabinoids have become increasingly popular for use in the treatment of a variety of medical and psychiatric disorders, however, their efficacy has not been previously assessed for the treatment of anxiety disorders.
- This systematic review and meta-analysis aimed to address this literature gap.
- Cannabinoid therapies were associated with statistically significant reductions in stress disorder symptoms, with an overall effect size of -1.85 (95% confidence interval [CI], -2.61 to -1.09). However, when correcting for publication bias, the effect was no longer significant.
- On the basis of the quantitative analyses that were possible, combined with general findings of the studies reviewed, this study indicates that preparations containing cannabinoids are of potential value but, given the limited evidence, this application of THC preparations should be considered experimental.
- Further studies should consider different preparations of THC, varying doses, longer durations of treatment, the use of adjunctive medications and therapies, and inclusivity of participants with psychiatric and medical comorbidities.

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INTRODUCTION

Anxiety disorders are disabling mental disorders characterized by significant feelings of fear, uncertainty, and worry with onset often before early adulthood.[1] As a group, anxiety disorders are the most prevalent of all mental disorders, with a lifetime prevalence as high as 31%.[2] Anxiety disorders are highly comorbid with depression, substance use disorders, personality disorders, as well as several medical conditions, including hyperthyroidism, cardiovascular disease, and asthma.[1] Given their high prevalence, when these disorders impair one's functional status and quality of life, there can be serious negative economic impacts to society as a whole.[1] As a result, effective treatments for these disorders are crucial and considered cost-effective.

Current first-line treatments for most anxiety disorders include cognitive behavioural therapy (CBT), selective serotonin-reuptake inhibitors (SSRIs), and serotonin-noradrenaline-reuptake inhibitors (SNRIs).[3] While most clinical trials for anxiety disorders document response rates between 50% to 60% and remission rates between 25% and 35%, refractory anxiety is as high as 20% at 5 years, and 30% at 10 years.[4,5] Although some evidence-based treatments for anxiety disorders are underutilized, as many as 30% of individuals with anxiety-related disorders remain refractory to first-line treatments.[6,7] Thus, there is an ongoing search for novel treatments that are effective and acceptable for patients.

Recently, cannabinoids have garnered attention for their treatment potential across both medical and psychiatric conditions.[8,9] The primary psychoactive ingredient in cannabis is tetrahydrocannabinol (THC), which acts on cannabinoid receptors to augment neurotransmitter release in the brain. Cannabidiol (CBD) is a non-psychotomimetic constituent of *Cannabis sativa* which has therapeutic potential as an antidepressant[10,11], antipsychotic[12–14], and anxiolytic.[15,16] Engaging the body's endocannabinoid system, cannabinoids appear to regulate many homeostatic processes to impact mood, anxiety, appetite, neurodevelopment, and fertility.[17,18] Considerable clinical and preclinical evidence has shown that cannabinoids, including THC and its synthetic analogues, exert a broad gamut of effects on emotional regulation, and can attenuate or exacerbate anxiety and fear-related behaviors.[19–25] Some of the available synthetic THC analogues include nabilone and dronabinol, which are used in a variety of conditions spanning neuropathic pain, as an antiemetic, for the treatment of movement disorders, and in the management of inflammatory bowel disease.[26,27] In contrast, nabiximols (Sativex®) is a mixture of THC and CBD, most commonly used in the treatment of spasticity from multiple sclerosis, but also in the management of cannabis use disorder.[28–30]

Available evidence indicates that there is a high degree of interindividual variability in the responses to cannabis is contributed by a wide spectrum of factors, including genetic and environmental determinants, as well as differences in the relative concentrations of THC and other alkaloids (such as cannabidiol) within the plant itself.[26]

Preliminary preclinical evidence suggests the therapeutic potential of CBD (and to a lesser degree, the use of other cannabinoids) as a treatment for generalized anxiety disorder (GAD)[31], panic disorder (PD)[32], social anxiety disorder (SAD)[33], obsessive compulsive disorder (OCD)[34,35], and posttraumatic stress disorder (PTSD).[36] Although clinical data is more limited, emerging evidence from human studies supports an anxiolytic role of CBD.[16,36] Available evidence suggests that CBD may enhance THC's antinociceptive and hypolocomotive effects, prolong THC's duration of action by inhibiting THC metabolism.[37,38] Some of the seminal literature on the use of CBD in particular suggests that CBD may be able to attenuate anxiety induced by exposure to THC in normal healthy participants as well as among those with an anxiety disorder.[11,31,33,39–42]

However, the extant clinical literature regarding clinical nuances—such as dose-dependent effects and more specific interactions between THC and CBD—is limited. While a recent meta-analysis by Black and colleagues explored the role of cannabinoids in the treatment of mental disorders and mental disorder symptoms—declaring that there is low quality evidence for the use of cannabinoids in any mental disorder—their review primarily focused on a single trial using nabilone for PTSD. Apart from this review, there have been no other formal meta-analyses exploring cannabinoid use in the treatment of anxiety disorder.

To that end, this systematic review and meta-analysis aimed to comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD, and their synthetic analogues—in reducing symptoms associated with anxiety disorders.

METHODS

Registration

This review is registered with the Open Science Framework (https://osf.io/gjc5u/), where a more detailed protocol can be found.

Data sources

This review adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[43] MEDLINE, EMBASE, PsycINFO, and Web of Science databases were searched from inception through August 2018 for published articles with data on the efficacy and acceptability of cannabinoids for the treatment of any anxiety disorder (including generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, and phobias). The search was updated in December 2019 to capture recently published articles since the initial search. The full search strategy is outlined in **Appendix 1** and the results of the search are displayed in **Figure 1.**

Study selection

Citations were imported directly into Covidence[44] – an online systematic review screening tool developed by the Cochrane Collaboration; this program facilitated the removal of duplicate citations. All reviewers independently assessed the titles and abstracts of records retrieved from the systematic search according to the identified inclusion and exclusion criteria, and discrepancies were resolved by consensus. Full-text articles were reviewed independently by two reviewers (A.B. and A.C.M.), and discrepancies were resolved by consultation with a third reviewer (E.R.H.) if needed. Our citation yield was supplemented by backward searching of the reference lists of included articles and by examining review articles for relevant primary studies.

Eligibility criteria

The population of interest for this study were adults with a clinician-diagnosed anxiety disorder (e.g., generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, obsessive compulsive disorder). We considered psychiatric and non-psychiatric samples as well as convenience samples from the community. Studies reporting the type and dose of cannabinoid medication used and the characteristics of participants treated were included; to that end, eligible studies did not have to be blinded randomized controlled trials to be included in the review. Eligible interventions involved any cannabis-based medications with the aim of reducing anxiety symptoms. Comparison interventions involved the use of different pharmacotherapies, placebo, or no pharmacotherapy (i.e. supportive care). Reference lists of articles and electronic sources of ongoing trials were also searched to yield 5 more studies, generating a total of 4809 articles after duplicates were removed.

Exclusion criteria included works that did not present original data (e.g., editorials, commentaries, and letters to the editor); case series or case reports; studies that did not present data pertaining to efficacy or acceptability of treatments for anxiety disorders (or where such data could be obtained); systematic reviews; studies where individuals were prescribed cannabinoids for other purposes or indications (e.g., chemotherapy-induced nausea or vomiting).

Data extraction

Two authors (AB and ACM) independently extracted key information and outcomes from the included studies. Outcomes included severity of anxiety symptoms, adverse effects, completion

of treatment, and engagement in follow-up treatment. Additional collected data included: sponsorship source, country, setting, author name, author institution, design/methods (study design and relevant grouping of participants), participants (baseline demographics, including age, sex, eligibility criteria for inclusion in the study), intervention (the name and identify of the cannabinoid agent used, the dose, frequency of administration, and route of consumption) and data were confirmed by consultation with a third author (ERH). Sufficient information was extracted from reports of included studies to enable assessment of the risk of bias. Where data reported by the primary study was incomplete, supplementary documents were searched to identify missing data and the primary study author was contacted by email where necessary.

Study quality and assessment of bias

Two authors (AB and ACM) independently used the Cochrane Risk of Bias Tool to appraise study quality and risk of bias.[45] In brief, the Cochrane Risk of Bias Tool addresses six specific domains in assessing the quality of randomized controlled trials: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues' (such as funding bias). Each included study was analysed and described according to these domains, and risk of bias plots were generated. Publication bias was assessed qualitatively by inspecting funnel plots for symmetry, as well as with statistical measures, including the trim-and-fill method[46], rank correlation test[47] and Egger's test.[48]

Statistical Analysis

We used Cochrane's Review Manager (Version 5.3) for random-effects meta-analysis [49]. For dichotomous outcomes, risk ratios (RR) were calculated with 95% confidence intervals (CI). For continuous data, outcomes were expressed as standardized mean differences (SMDs) with 95% CI. If studies involved more than two treatment arms (e.g., two different active medications and placebo), the active medications, compared to placebo, were included in separate subgroups and the calculation of overall totals was suppressed thereby avoiding the unit of analysis error of double-counting participants. Clinically relevant heterogeneity was assessed by reviewing the variations between studies in terms of the characteristics of participants included, the interventions, and the reported outcomes. Statistical heterogeneity was measured using the Chi^2, tau, and I^2 statistics[50] and by visual inspection of the forest plots.[51] A p-value of the Chi^2 test lower than 0.05 or an I^2 statistic of at least 50% indicated a significant statistical heterogeneity. To identify potential sources of heterogeneity, we considered sensitivity analyses, leave-out-one meta-analysis, comparisons with fixed-effects meta-analyses estimates, and subgroup analyses. For example, we stratified results from randomized controlled trials and quasi-experimental observational studies given the methodological differences in these study designs.

RESULTS

Our search strategy identified a total of 3754 unique citations, of which 42 were reviewed in full. Although fourteen studies were considered eligible for qualitative synthesis, only eleven reported meta-analysis compatible outcomes (**Figure 1**).[31,33,39,52–58] Specifically, the three studies[2,58,59] left out of the meta-analysis used subjective reports of improvement (rather than specific instruments). However, all fourteen studies are described in **Table 1**.

Participant and study characteristics

Across studies, a total of 1548 individuals with a physician-diagnosed anxiety disorder were captured by this meta-analysis (**Table 1**). The median age was 33 years (interquartile range [IQR] = 28 to 44) and primarily male (66%). The anxiety disorders considered were PTSD (n=8), GAD (n=4), and SAD (n=2). With the exception of one study[58], all studies excluded participants with significant psychiatric or medical comorbidity, such as bipolar disorder or schizophrenia. Reporting of other study demographics was largely incomplete, with most studies not providing ethnicity, comorbidity, educational attainment, or other relevant descriptors of the studied participants. Studies were undertaken in North America (n=10), Brazil (n=3) and Israel (n=1), with substantial variation in sample size (from n=8 to n=831). Of the included studies, five were randomized controlled trials, six were open-label trials, and three were quasi-experimental cohort studies; two were conducted retrospectively, with the remaining twelve being conducted prospectively. Study duration ranged from 1 to 104 weeks (median = 16). Experimental cannabinoid preparations included nabilone (n=5), tetrahydrocannabinol [THC] (n=6), and cannabidiol [CBD] (n=3).

Assessment of study quality and bias

The evidence provided in this study is current to July 2019. The quality of evidence among the primary and secondary outcomes was low to moderate (**Appendices 2, 3)**, suffering from several serious methodological limitations, particularly blinding of the participants (owing to the subjective effects of cannabis products). Randomization was not consistently done across studies as there were only three randomized controlled trials, with no single trial assessing all the outcomes of interest. This, in addition to high heterogeneity in the interventions of interest and anxiety disorder groups, contributed to great variability. The rate of attrition was not particularly high, and most studies discussed participant flow through the study. We found little evidence of selective reporting or selection bias.

C**annabinoid treatment reduces symptoms in anxiety disorders and is concordant with clinically significant improvements**

Eleven studies were combined using a random-effects meta-analysis, with a pooled SMD of -1.85 (95% confidence interval [CI], -2.61 to -1.09; I^2 = 94.6%, 11 studies, **Figure 2**) with cannabinoids relative to the control groups of the individual studies. When RCTs and observational studies were separated, we found no difference in the effect sizes, indicating continuity across designs. This overall finding of statistical significance was in agreement with clinically significant or meaningful reductions in anxiety symptoms in all but one study, where the study authors reported that there was a worsening in PTSD symptoms with cannabinoid use.[58]

Efficacy of cannabinoids for post-traumatic stress disorder

All eight PTSD studies found evidence for the efficacy of cannabinoids across various types of preparations for the treatment of PTSD symptoms. Greer et al[55] identified a 75% reduction in Clinician Administered PTSD Scale [CAPS] symptom scores for participants using cannabis provided by a medical marijuana dispensary. Cameron et al[54] found that nabilone (at varying doses) effectively treated multiple symptom domains of PTSD, including a reduction in the number of nights of nightmares per week, scores on the PTSD Checklist [PCL-C], the Global Assessment of Function Scale [GAF], and self-reported insomnia. Similarly, Fraser et al [59] found that nabilone at a dose of 0.5 mg/day was effective at reducing nightmare symptoms in those with poorly-controlled PTSD when using standard pharmacotherapy. Jetly et al[57] further strengthened the case for nabilone's effectives, finding a significant improvement among military personnel with PTSD via reduced CAPS scores, as well as increased Clinical Global Impression [CGI] scores, indicating improved functioning. In Israel, Roitman et al[56] used adjunctive dronabinol (also known as 'liquid THC') at a dose of 5 mg, twice-daily (10 mg in total per day), finding that this caused a statistically significant improvement in global PTSD symptom severity, sleep quality, frequency of nightmares, and hyperarousal symptoms. For the six studies reporting pre-post differences in the PTSD symptom severity, cannabinoid treatment was associated with a reduction in PTSD symptom severity (SMD: -1.78, 95% CI, -3.04 to -0.52, I^2 = 97.8%, six studies, **Figure 2**).

Efficacy of cannabinoids for social anxiety disorder

The two studies looking at the use of cannabidiol for social anxiety disorder [31,33] found that CBD doses ranging from 400 to 600 mg/day effectively reduced anxiety symptoms in study participants on the basis of subjective ratings on the Visual Analogue Scale [VAS]. CBD was associated with a significantly greater improvement in the anxiety factor of a 100-point visual analogue mood scale compared to placebo (p=0.01) and a significant increase in SSPS-N for placebo group; however, there was no difference between CBD-treated and healthy controls. Crippa et al[31] found a significant decrease in subjective anxiety (p<0.001) with CBD. Additionally, there was reduced activity in left para-hippocampal gyrus, hippocampus, and inferior temporal gyrus (p<0.001) with increased activity in right posterior cingulate gyrus (p<0.001). The pooled SMD in the VAS score before and after treatment indicates that CBD was associated with a reduction in symptoms associated with SAD (SMD: -2.20, 95% CI, -4.25 to -0.15, I^2 = 85.7%, 2 studies, **Figure 2**).

Efficacy of cannabinoids for generalized anxiety disorder

Four studies explored cannabinoids in the treatment of generalized anxiety.[39,52,53,60] Three[39,52,60] of four studies found cannabinoids had significant anxiolytic effects. Fabre et al[52] identified a statistically significant improvement in anxiety symptoms in the nabilone group versus those receiving a placebo (p<0.001). Zuardi et al[39] found that cannabidiol attenuated THC-induced anxiety effects. Wan et al[60] found that nearly 30% (87/287) of participants receiving medical marijuana reported significant reductions in self-reported anxiety symptoms. However, Glass et al[53] did not find that nabilone had significant anxiolytic effects. For the three studies reporting pre-post differences in the severity of generalized anxiety symptoms[39,52,53], cannabinoid treatment was associated with a reduction in the severity of GAD symptoms (SMD -1.77, 95% CI, -2.42 to -1.13, I^2 = 0.0%, 3 studies, **Figure 2**). Additionally, for the two studies[39,60] reporting dichotomous improvements in anxiety symptoms, the relative risk (RR) of subjective improvement in anxiety was 2.01 (95% CI, 1.43 to 2.83, I^2 = 51%, 2 studies, **figure not shown**)

Acceptability and tolerability of cannabinoids for anxiety disorder symptoms
Data on the number of participants experiencing adverse events was inconsistently reported. Only a small number of adverse events were reported in total, and no serious adverse events were reported — which we defined as symptoms or signs requiring acute hospitalisation or emergency intervention. Dry mouth, dry eyes, headaches, presyncope, and drowsiness were more frequently experienced by nabilone users in two of the studies.[52,53] However, the other two nabilone studies[54,57] did not report any adverse events. Cannabidiol was relatively well-tolerated, with only one study reporting participants to experience more sleepiness than the control.[39]

Publication bias
Risk of publication bias was assessed graphically using funnel plots, depicted in **Figure 3** and was deemed high owing to the grossly asymmetric appearance of the plots. Statistical tests for publication bias completed using the linear regression test of funnel plot asymmetry confirmed the gross asymmetry of the funnel plots (p=0.01) were statistically significant. Accordingly, the trim-and-fill method was applied, with an estimate of 6 missing studies required to correct the asymmetry in the funnel plot. Consequently, crude effect sizes were substantially inflated by publication bias; after correction, the overall effect of cannabinoids for anxiety disorder symptoms was no longer statistically significant (g = -0.38 [95% CI, -1.28 to 0.52]).

Assessment of heterogeneity
Using several pre-specified subgroup and meta-regression analysis, we tested the contributions of several covariates to explain observed heterogeneity. While there were increasing effect sizes for younger patients (p<0.01; **Appendix 4**) and for longer durations of treatment (p<0.01; **Appendix 4**), there were no differences in effect sizes by sex, cannabinoid type, anxiety disorder subtype, or cannabinoid dose.

DISCUSSION

Summary

Fourteen studies were identified by this systematic review of which 11 contributed to a formal meta-analysis with the aim of measuring the efficacy and acceptability of cannabinoid therapies for the treatment of anxiety disorders. Our study demonstrates that there is some evidence for the efficacy of nabilone, cannabidiol, and tetrahydrocannabinol for the treatment of posttraumatic stress disorder, social anxiety disorder, and generalized anxiety disorder. However, this evidence is marred by many methodological issues, notably publication bias, which when corrected for led to a loss of statistical significance in the main outcome. Nevertheless, there was fairly consistent evidence for a reduction in anxiety symptomology with the use of cannabinoid therapies as reported by individual studies—with the exception of one study that found PTSD symptoms were worse with cannabinoid use. As well, there is evidence that cannabinoid treatments were fairly well-tolerated by study participants, with few dropouts due to adverse events. However, significant heterogeneity was identified, likely due to study-specific differences in the types of preparations used, the disorders considered, the duration of treatment, and the design of the component studies. This heterogeneity may account for significant variability across studies and undermines the quality of the evidence presented here. Furthermore, inconsistent reporting of adverse events across studies is another limitation given the established evidence of cannabinoid-related adverse events—especially in young people—related to psychosis[61] or cannabinoid withdrawal.[62]

Clinical implications of findings

Most of the individual studies considered in this review identified positive signals indicating cannabinoid efficacy for anxiety disorder management. However, only preliminary evidence was found at the meta-analysis level to indicate that preparations containing THC, nabilone, and cannabidiol have therapeutic potential for the treatment of anxiety disorders in adults. For example, our findings are consistent with a recent report published by an expert, ad hoc committee of the National Academies of Sciences, Engineering, and Medicine National Academies, which states that there is limited evidence for cannabinoids in the treatment of poor appetite, Tourette syndrome, anxiety, posttraumatic stress disorder, cancer, irritable bowel syndrome, epilepsy and a variety of neurodegenerative disorders.[63] To that end, the extant evidence is not sufficiently comprehensive to advise on the combination of cannabinoid treatments with established anxiolytics. For example, the use of cannabinoids alongside concomitant psychotropic drugs increases the potential for a range of clinically-significant drug-drug interactions, which should be considered when making treatment recommendations.[64]

Strengths

Our study should be noted for a few of its strengths. First, we used a comprehensive, up-to-date search strategy, which helped us identify nearly five thousand citations. Second, our strategy had a low risk of publication bias, as indicated by both qualitative and quantitative assessments. Third, our study provides a novel perspective, as it is the first quantitative meta-analysis exploring the utility of cannabinoids for the treatment of anxiety and of anxiety disorders. As such, it complements and provides evidence for previous reviews (either systematic or narrative) that have either explored the use of cannabinoids for medical conditions or psychiatric illnesses in general. Fourth, the findings presented here are largely consistent with those of the component trials synthesized in our meta-analysis, which prevents distortion of findings of individual studies

when estimates are pooled, but also, with a previous systematic review.[41] However, there is some disagreement with a more recently published systematic review that explored the use of cannabinoids broadly across a range of medical and psychiatric conditions.[26]

As a minimum of four weeks is generally considered necessary for the achievement of a partial response to standard antidepressant medications for anxiety disorders, longer durations of studies would be helpful in evaluating the effectiveness of cannabis preparations. Overall, the studies were of relatively short duration, ranging from a few hours to two years' worth of follow-up. However, cannabis preparations can be subjectively felt within minutes to hours of administration and have different mechanisms of action than typical pharmacological treatments for anxiety. Longer treatment windows and/or study durations would further characterize the duration of cannabinoid efficacy as well as exploration into their tolerability and the occurrence of adverse events. Sustained treatment, in conjunction with psychological therapies, may unmask the greater efficacy of THC preparations on symptoms of anxiety. Unfortunately, with the rigorous scientific study of cannabis as a medicine being hampered by production restrictions, federal regulations, and public stigma, so much remains unclear regarding how effective cannabis truly is for various medical conditions. As cannabis is becoming increasingly legalized in many settings, research in the field is on the rise, particularly in Canada and the United States.

Limitations

While our findings are of interest to the research community exploring novel treatments for anxiety and of anxiety disorders, they should be interpreted in the context of several significant limitations. First, this meta-analysis considered multiple study designs—randomized controlled trials, open-label studies, and quasi-experimental designs—and multiple study durations (ranging from one to 104 weeks). To that end, the short duration of some studies and very long duration of others makes arriving at a clear conclusion regarding optimal treatment timelines more challenging. As a result, the combination of such studies to create pooled estimates may appear to be a statistical violation at first glance—however, when we explored the contributions of study design and cannabinoid subtype to heterogeneity by way of subgroup analyses, we found minimal evidence for this, suggesting the decision to be inclusive was fair.

Second, the studies included in this review were often small, with the smallest having a sample size of only 8 participants; as a result, the precision of individual estimates is questionable. To that end, the sample sizes for the randomized controlled trials were so small that the total number of participants across all five of them was only 80. With that said, one of the strengths of meta-analysis is the ability to pool many small studies together to overcome the limitations of small sample size in any one study. Still the low study yield precluded the extent of meta-analysis that could be done, as well as the extent to which we could explore sources of heterogeneity.

Third, the quality of evidence was assessed as generally low: few studies were truly randomized, controlled, or blinded with any degree of certainty. However, even in ideal circumstances, it would be difficult to control for blinding given that participants can almost immediately 'feel' the subjective psychotropic effects of cannabinoids.

Fourth, while all included studies involved a cannabinoid preparation, there was tremendous diversity in the types of preparations, doses, routes of administration (oral versus smoked), and duration of treatment. Given the differential effects of THC and CBD on anxiety, it may have been statistically inappropriate to combine effects from studies that examined THC with those that examined CBD. However, the only measured covariate that was associated with

heterogeneity (between study variance) in results was in the duration of treatment and participant age. This suggests that our findings are somewhat robust to the specific composition of the cannabinoids considered. Nonetheless, the review provides an overview of the current status of evidence and points to future directions for research on the development of cannabis-based pharmacotherapies for anxiety disorders.

Future Research

Given the lack of consensus findings regarding cannabinoids for anxiety, some suggestions for future research are outlined here. Large, double-blinded, randomized, placebo-controlled trials are needed in order to provide high quality evidence on the efficacy and acceptability of cannabinoids for the treatment of anxiety. Head-to-head studies would be helpful in elucidating the comparative performance of different cannabinoids (e.g., THC vs. CBD). Further studies should compare the effectiveness of different preparations, doses and duration of treatment, adjunct medications and therapies, and could explore additional types of anxiety disorders that have not yet been researched, such as OCD and Panic Disorder. At this point in time, established pharmacotherapies and psychological approaches should remain the mainstay of anxiety disorder treatment until more robust studies are done using cannabinoid therapies.

Conclusions

This meta-analysis demonstrates that in treating symptoms associated with anxiety disorders, the evidence is incomplete for the cannabis-based pharmacotherapies identified. The quality of evidence for many of the outcomes was downgraded due to small sample size and inconsistency. The general findings reported by the studies reviewed indicate that nabilone, cannabidiol, and THC are potentially of some value in the treatment of SAD, GAD, and PTSD in terms of reducing the severity of anxiety symptoms and acceptability of treatment; however, the overall effect was diminished when corrected for publication bias. Across studies, no serious adverse events were reported with any of the cannabis preparations used, suggesting that these are potentially well-tolerated as medications; however, adverse events were inconsistently reported across studies, which suggests that the true tolerability may be lower than reported here. Hence, preparations containing cannabis are of potential value but the limitations in the evidence of application of cannabis preparations should be considered to be experimental until further research is conducted.

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Table 1. *Characteristics of Included Studies*

Study	Design	Duration	Study Sample	Intervention	Outcomes	Findings
Fabre 1981	RCT	4 weeks	GAD (n = 20, 75% female, mean age = 29.5 years)	Nabilone 1 mg po TID *vs*. placebo	HARS, AE	Improved anxiety but more dry eyes and dry mouth in nabilone group
Glass 1981	RCT	1 week	GAD (n = 8, 38% female, mean age = 26.0 years)	Nabilone 2 mg po OD *vs*. placebo	Physiologic, AE	More light-headedness and headaches with nabilone without significant anxiolytic effects
Zuardi 1982	RCT	1 week	GAD (n = 8, 75% female, mean age = 29.0 years)	CBD 1 mg/kg po OD	STAI, AE	CBD attenuated THC-induced anxiety effects; however, also increased sleepiness
Fraser 2009	Open-label	1 year	PTSD (n = 47, 43% female, mean age = 44.0 years)	Nabilone 0.5-6 mg po OD	Nightmares, AE	Improvement in nightmare symptoms, sleep, flashbacks, and night sweats
Bergamaschi 2011	RCT	1 week	SAD (n = 24, 50% female, mean age = 23.5 years)	CBD 600 mg po OD *vs*. placebo	VAMS, SSPS-N, physiologic	Significant improvement in anxiety with CBD vs. placebo (p = 0.01).
Crippa 2011	RCT	1 week	SAD (n = 10, 0% female, mean age = 24.2 years)	CBD 400 mg po OD *vs*. placebo	VAMS	Significant decrease in subjective anxiety ($p<0.001$))
Reznick 2011	Open-label	2 years	PTSD (n = 80, age and sex not described)	THC (2-3 grams smoked OD)	CAPS, QOL, pain scores	Improvement in QOL, pain, PTSD symptoms, and reduced analgesic use
Massiah 2012*	Open-label	1 year	PTSD (n = 29, 0% female)	THC (23% smoked OD)	CAPS	Significant improvement in PTSD symptoms
Cameron 2014	Cohort	11 weeks	PTSD (n=104, 0% female, mean age = 32.7 years)	Nabilone	PCL, GAF, AE	Significant improvement in mean PCL score, nightmares, sleep, and GAF (p=0.001)
Greer 2014	Cohort	2 years	PTSD (n=80)	THC smoked OD	CAPS	Mean CAPS total score reduction of 76.3 points
Roitman 2014	Open-label	3 weeks	PTSD (n=10, 30% female, mean age = 52.3 years)	THC 5-10 mg po OD	CAPS, PSQI, CGI, NFQ	Significant improvement in sleep quality, nightmares, and global functioning
Jetly 2015	RCT	16 weeks	PTSD (n=10, 0% female, mean age = 43.6 years)	Nabilone 0.5-3 mg po OD *vs*. placebo	CAPS, CGI, WBQ	Significant improvement in nightmares, global functioning, but no improvement in sleep
Wilkinson 2015	Cohort	19 weeks	PTSD (n=831, 69% female, mean age = 51.8 years)	THC smoked OD	M-PTSD	Mild improvement in M-PTSD symptom score in those initiating cannabis use on program end
Wan 2017	Open-label	10 months	GAD (n=287, 31.2% female, mean age = 44.9 years)	THC smoked OD	Self-reported anxiety symptoms	30.3% reported improvement in anxiety with medical marijuana.

RCT = randomized controlled trial; GAD = generalized anxiety disorder; TID = thrice daily; HARS = Hamilton Anxiety Rating Scale; OD = once daily; AE = adverse events; CBD = cannabidiol; STAI = State-Trait Anxiety Inventory; VAMS = Visual Analogue Mood Scale (anxiety factor); PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; SSPS-N = Self-Statements During

Public Speaking Scale; CAPS = Clinician Administered PTSD Scale; QOL = quality of life; THC = tetrahydrocannabinol; GAF = Global Assessment of Functioning; PSQI = Pittsburgh Sleep Quality Index; NFQ = Nightmare Frequency Questionnaire; CGI = Clinical Global Impression; WBQ = Well Being Questionnaire; M-PTSD = Mississippi Scale for Combat-related PTSD

FIGURE LEGENDS

Figure 1. The above flow diagram outlines the systematic review process as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Figure 2. The above forest plot depicts effect sizes for reduction in anxiety symptoms across studies. The diamonds represents the across-study pooled estimates, while the squares represent the estimate from each individual study. The horizontal lines are the 95% confidence intervals for the effect size. Confidence intervals that intersect the line of no effect (standardized mean difference = 0) are nonsignificant.

Figure 3. The above funnel plot depicts the standard error across the effect sizes reported by individual studies. The gross asymmetry of the plot indicates significant publication bias risk.

Figure 4. The above bubble plots depict the relationship between effect sizes for reducing anxiety symptoms by the age of the study sample (above) and the duration of treatment (below). The plots demonstrated that younger patient samples and longer durations of treatment were associated with greater treatment effect sizes.

Figure 1. *PRISMA Study flow diagram.*

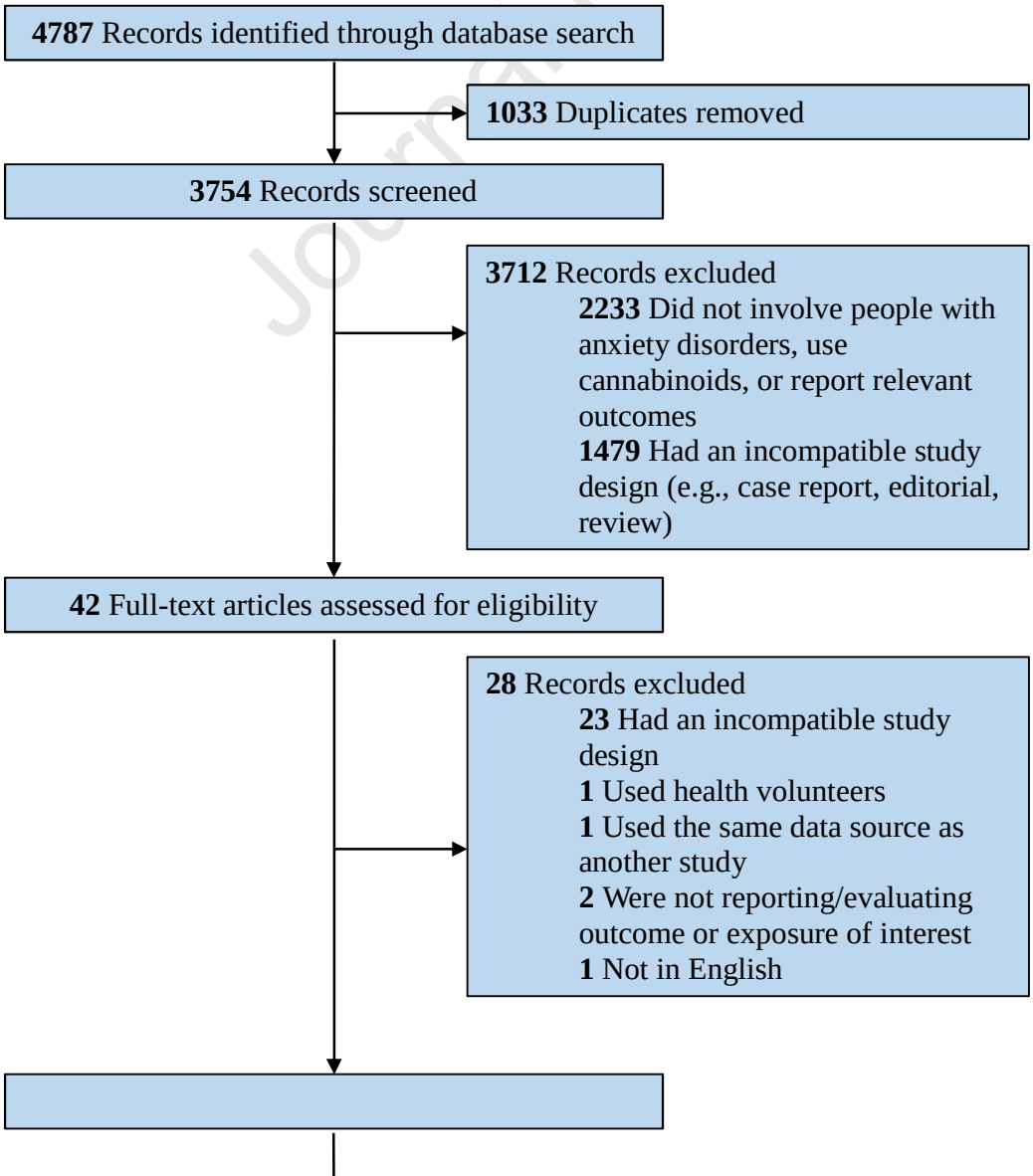
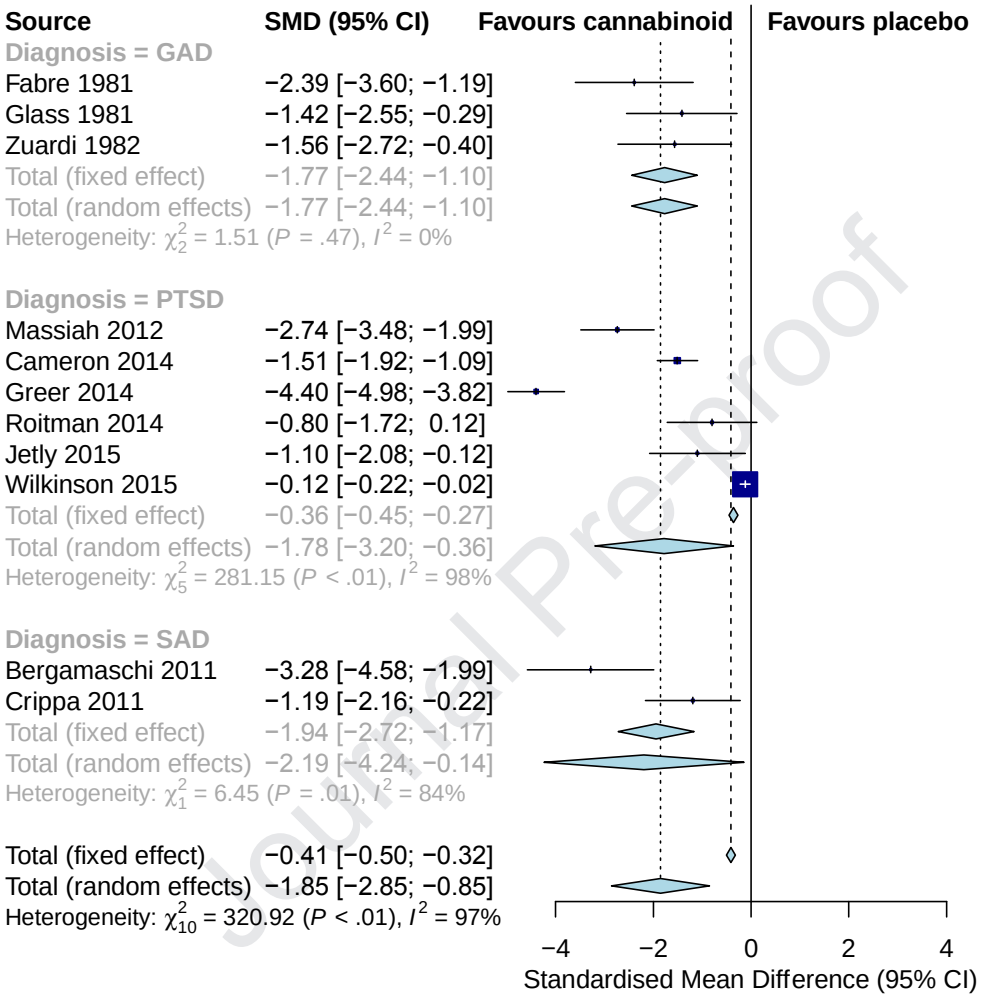
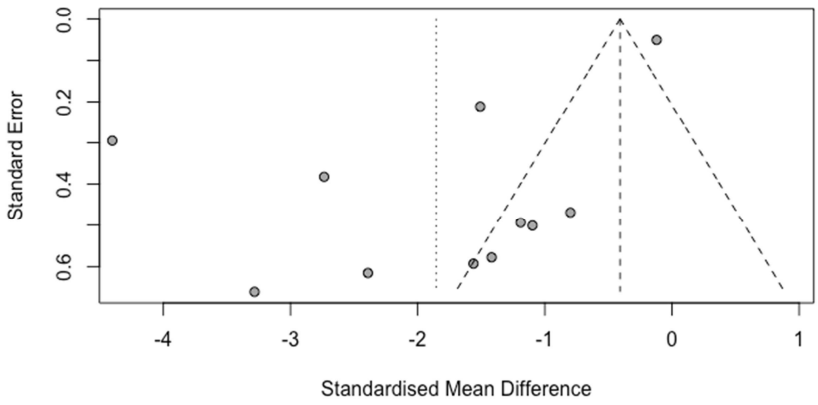


Figure 2. Random-effects meta-analysis of overall standardized mean difference in anxiety disorder symptom scores with cannabinoids before-and-after treatment and by subgroups for social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD).



SMD = standardized mean difference; CI = confidence interval; P = probability that observed estimate occurred by chance alone (higher indicates a larger chance that the finding occurred by chance); I^2 = Higgin's heterogeneity statistic (higher indicates greater heterogeneity).

Figure 3. *Risk of publication bias depicted with funnel plots for efficacy of cannabinoid preparations for anxiety disorders.*

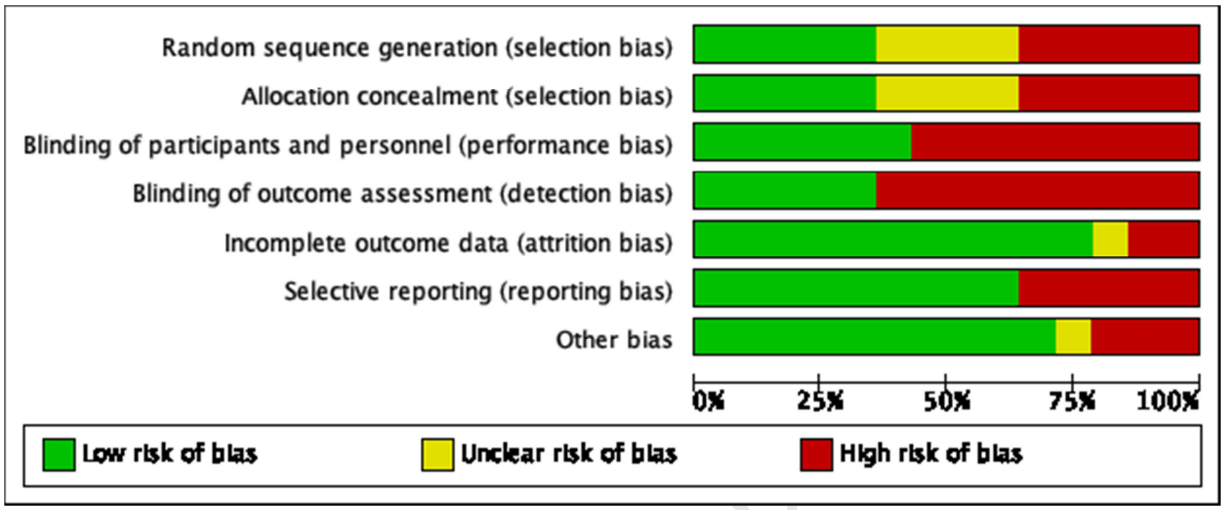


APPENDICES

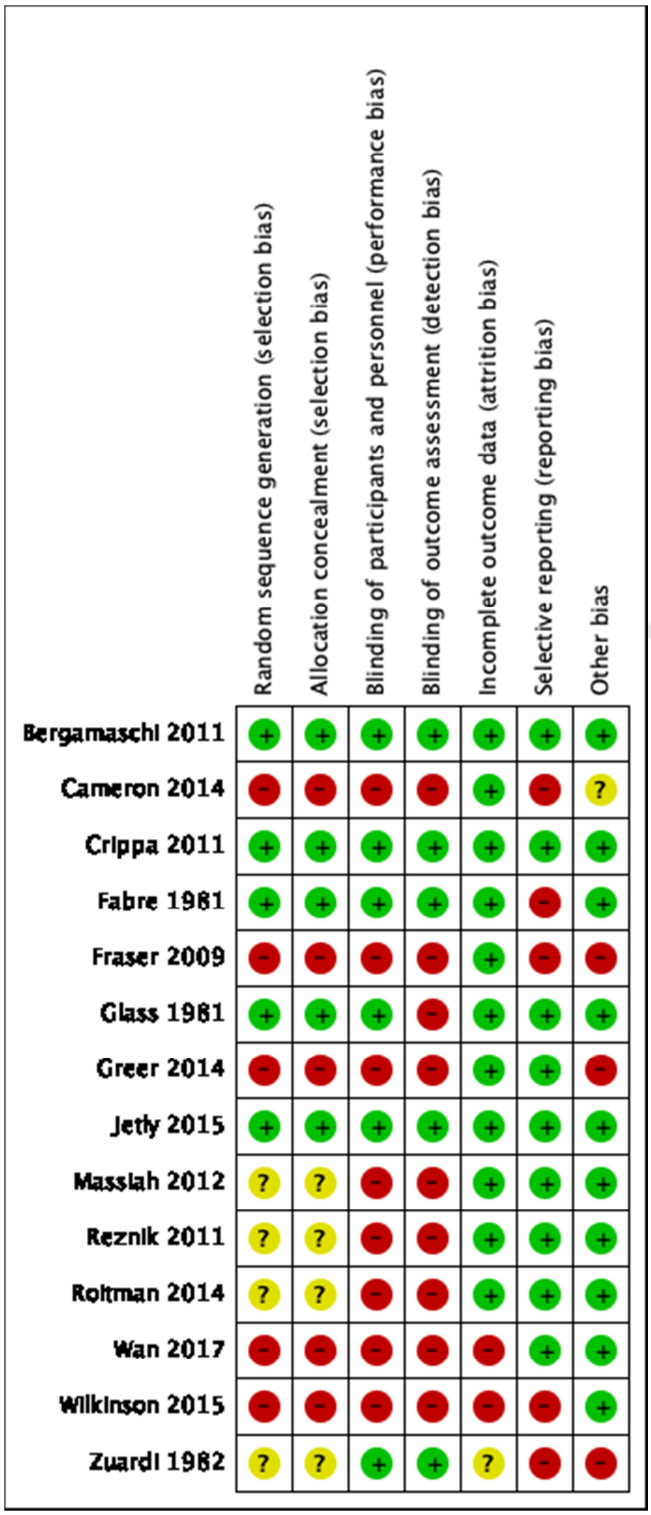
Appendix 1. *Search Strategy*

1. Agoraphobia OR Separation Anxiety OR Neurocirculatory Asthenia OR Neurotic Disorders OR OCD OR Panic Disorder OR Phobic Disorders OR Acute Stress Disorder OR Anxiety Neurosis OR Anxiety Disorder*.ab,ti.
2. Cannabis OR Cannabinoids OR Cannabi*.ab,ti. OR Marijuana OR Marijuana/Cannabis Abuse/Addiction OR Marijuana/Cannabis Use OR Medical Marijuana OR Cannabis/Marijuana Smoking OR THC OR Marijuana*.ab,ti.}
3. 1 and 2
4. Limits: English, Humans
    a. MEDLINE: 509, 3 removed duplicates, 506 added, 506 total
    b. OVID PsycINFO, 421 Results, 215 removed duplicates, 206 added, 712 total
    c. EMBASE 1, 999 Results, 150 removed duplicates, 849 added, 1561 total
    d. EMBASE 2, 1000 Results, 164 removed duplicates, 836 added, 2397 total
    e. EMBASE 3, 993 results, 149 removed duplicates, 844 added, 3241 total
    f. Web of Science, 865 Results, 352 removed duplicates, 513 added, 3754 total

Appendix 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Appendix 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Appendix 4. Bubble plot of meta-regression of age (upper) and weeks of follow-up (bottom) against standardized mean difference of efficacy of cannabinoids for the treatment of anxiety disorders.