The role of cannabis in treating anxiety: an update

Michael Van Ameringen[a,b], *Jasmine Zhang*[b], *Beth Patterson*[a,b], *and Jasmine Turna*[b,c,d]

Purpose of review
Cannabis use for medical purposes has become increasingly common, including as treatment for mental health disorders such as anxiety. Unfortunately, the evidence examining its use in mental health has been slow to evolve, but is emerging. Given the widespread use of cannabis, it is important for both clinicians and those who suffer with anxiety to understand the effects of cannabis on symptoms of anxiety. In this review, we present recent, available evidence from animal models, clinical trials, and survey studies and evaluate the contribution of these studies to the current understanding of the role of cannabis in treating anxiety.

Recent findings
In reviewing recent evidence, we observed significant inconsistencies across findings from preclinical studies. Large-scale surveys suggest that cannabis may be effective in reducing anxiety, however, these results stand in contrast to equivocal findings from clinical trials.

Summary
The literature evaluating the efficacy of cannabis in anxiety disorders is in its infancy. The survey data is generally positive. Although, while some animal studies posit cannabis constituents to have anxiolytic effects, others suggest the opposite or null results. Few new clinical trials have been conducted recently, and the extant trials have significant flaws in methodology. Although anecdotal evidence from survey studies, and a small signal found in animal studies and single-dose clinical trials provide early support that cannabis may be effective for alleviating anxiety, ultimately, the current evidence is equivocal. More high-quality clinical trials must be published before sound conclusions regarding the efficacy of cannabis for treating anxiety can be drawn.

Keywords
Δ^9-tetrahydrocannabinol, anxiety, cannabidiol, medical cannabis

INTRODUCTION

Anxiety disorders are among the most prevalent mental health conditions, affecting 264 million individuals worldwide in 2017 [1], with large-scale general population estimates suggesting 12-month prevalence rates of 18.1%–22.2% [2,3]. Although a wide range of treatments exist for anxiety disorders, only 40%–60% of patients exhibit adequate responsiveness to first-line interventions such as medications and cognitive behavioural therapies [4], highlighting the need for alternative treatments.

In recent decades, cannabis has become increasingly popular as an alternative treatment for anxiety symptoms and disorders. Many countries have legalized both recreational and medical cannabis, and individuals continue to use cannabis in regions where it remains an illicit substance. Estimates suggest that approximately 5.1% (28 million) of individuals aged 15–64 in the European region used cannabis in 2016 [5▪]. In the last 4 months of 2018, 1.09 million Canadians used cannabis for solely medical purposes whereas another 1.27 million used cannabis both medically and recreationally [6]. The surge in medical cannabis use has propagated research regarding its mechanism of action, safety, and efficacy. Although many patients

[a]Department of Psychiatry and Behavioural Neurosciences, McMaster University, [b]MacAnxiety Research Centre, McMaster University MacAnxiety Research Centre, McMaster University, [c]Michael G. DeGroote Centre for Medicinal Cannabis Research and [d]Peter Boris Centre for Addictions Research, McMaster University & St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada

Correspondence to Michael Van Ameringen, 1057 Main St, W L02 Hamilton, ON L8S 1B7, Canada. Tel: +1 289 396 4242; fax: +1 289 396 0309; e-mail: vanamer@mcmaster.ca

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KEY POINTS

- Cannabis has been legalized for both recreational and medical use in many places across the world and survey studies suggest that people are using cannabis to treat their anxiety.
- Although animal models have demonstrated a signal for the therapeutic effect of cannabis in treating anxiety, there have been conflicting results surrounding the actions of specific constituents and dosages.
- The few extant clinical trials in human subjects do not support the anxiolytic effects of cannabis, but their conclusions are limited by shortcomings in experimental design.
- Future research should involve high-quality clinical trials in anxiety disordered populations, using larger sample sizes and control conditions, lowering the risk of bias.

report using cannabis to treat their anxiety, little evidence supports its efficacy. Nevertheless, anecdotal reports of the success of cannabis in treating anxiety disorders has garnered the attention of researchers and healthcare professionals, as suggested by newly emerging preclinical studies and clinical trials. As such, the goal of the current review is to examine the recent evidence comprised of work in animal models, clinical and nonclinical samples and survey studies, and evaluate its contribution to our understanding of cannabis for treating anxiety.

Δ^9-TETRAHYDROCANNABINOL AND CANNABIDIOL

Although over 100 phytocannabinoids have been isolated from the cannabis plant [7▪], two constituents have been the focus of mechanistic investigation and interactions with body systems: Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a partial agonist for cannabinoid receptor-1 (CB_1R) and cannabinoid receptor-2 (CB_2R), the two primary G-protein coupled receptors of the endocannabinoid system [8▪]. THC's psychoactivity is largely because of its agonist effects at CB_1R and interaction with CB_2R is thought to mediate its immunological or anti-inflammatory effects [8▪]. On the other hand, CBD was originally proposed to be a negative allosteric modulator of CB_1R and CB_2R, however there are numerous non-endocannabinoid systems it may interact with to explain its vast array of biologic effects [8▪]. Recent findings have pointed to specific interactions between CB_1R, 5-HT_{1A} serotonin receptors, and transient receptor potential vanilloid type 1 receptors [8▪,9,10▪]. The various interactions of CBD and THC with the endocannabinoid system have connected them closely with emotion regulation and anxiety management [10▪].

THE EFFECTS OF CANNABIS IN ANIMAL MODELS OF ANXIETY

Animal models are typically the first venture into clinical research. In preclinical anxiety research, the most common paradigm used is the Elevated Plus Maze (EPM), which exploits a conflict between rodents' innate tendency to explore novel environments and their fear of bright, elevated environments [9]. In the EPM, mice are placed on an elevated platform consisting of four sections arranged in a 'plus'-shaped formation with two open and enclosed arms. More time spent in the 'open', low-walled arms is indicative of lower anxiety [9].

The literature has generally described CBD to be anxiolytic in mice [reviewed in 9▪] rather than the contrary [9,11]. More specifically, a bell-shaped dose-response curve has been described of CBD's effects on anxiety: moderate doses show anxiolytic effects, while higher doses have minimal effect [9]. However, studies published in the past year draw a more equivocal conclusion. In one study, mice who received a single dose of 20 mg/kg CBD explored the open arms of the EPM significantly longer than those treated with placebo or 5 mg/kg, signifying an anxiolytic effect of 20 mg/kg CBD [12▪]. In a different study, mice were injected with placebo or 20 mg/kg CBD daily for 6 weeks [7▪]. Within both groups, some mice began treatment at 3 months old whereas others began treatment at 5 months old. At 6 months of age, all mice were test for a range of physiological and behavioural functions, including anxiety. In the EPM, only mice who received CBD starting at 5 months of age spent more time in the open arms compared to the placebo group [7▪]. These studies suggest that a high dose of CBD may have anxiolytic potential, but effects may vary based on treatment duration.

Another EPM study suggested that CBD's anxiolytic effect may only be relevant when in the presence of THC [13▪]. Mice were injected with various concentrations of THC, CBD, combined THC and CBD, or a vehicle control. Based on the EPM, the anxiety levels of mice injected with 100 ng/500 nl CBD did not differ from the control group. On the contrary, mice injected with 100 ng/500 nl THC spent significantly less time in the open arms of the maze compared to control mice, supporting a previously documented anxiogenic effect of THC [14]. In CBD and THC co-administration, 100 ng/500 nl CBD did not affect THC-induced anxiety, while 500 ng/500 nl CBD appeared to block the

anxiogenic effect of 100 ng/500 nl THC [13▪]. Another study explored the effect of synthetic cannabinoids (AB-FUBINACA, TAB-CHMINACA, and PB-22; potent CBR1 and CB2R agonists) and THC on anxiety using the EPM. Treatment with all compounds led mice to spend more time in the open arms of the maze compared to vehicle controls [15▪]; however, the anxiolytic effects were dose-dependent. For instance, AB-FUBINACA was anxiolytic anxiety at 3 mg/kg but anxiogenic at 4 mg/kg; only 1 mg/kg AB-CHMINACA showed anxiolytic effects, while PB-22 significantly decreased anxiety at 0.05, 0.1, and 0.4 mg/kg doses. THC demonstrated anxiolytic effects at a high dose of 25 mg/kg, which contradicts the general understanding that THC is anxiogenic [9,14].

PHARMACOKINETICS

The pharmacokinetic properties of CBD have been examined in humans. A recent review assessed these properties based on various methods of administration, including oromucosal spray, oral administration, intravenous administration, and smoking [16▪]. Results indicated the half-life of CBD to be between 1.4 and 10.9 h after oromucosal spray, 2 and 5 days after chronic oral administration, 24 h after intravenous administration, and 31 h after smoking [16▪]. The bioavailability of CBD after smoking was 31%, although this may be influenced by characteristics of puffs, inhalation volume, inhalation hold time, and drug reward expectations [17]. Bioavailability results from other routes of administration were not available, indicating an area requiring more research. The area-under-the-curve (AUC) for the plasma concentration vs. time graph and C_{max}, which indicates the highest plasma concentration measured over a certain time span, both increased in dose-dependent manners [16▪]. However, little information has been published regarding the percentage binding of CBD to target receptors, perhaps because its binding mechanisms and receptor interactions are not fully understood.

CANNABIS IN CLINICAL TRIALS

Despite the potential anxiolytic effects of cannabis constituents observed in animal models, results from clinical trials in humans have been largely inconclusive. Critically, prospective examinations of the cannabis plant in anxiety disordered population simply do not exist; however, a small literature examining cannabis-related compounds has been noted [18▪,19▪,20▪]. Nabilone, a synthetic cannabinoid, was found to be effective for reducing anxiety in both an open-label and a double-blind study [21]. However, a single-dose of 1–5 mg nabilone was ineffective for four anxious volunteer individuals [22]. More recently, a study of nabilone in patients taking antidepressant medications for mixed anxiety and mood disorders showed significant improvements in anxiety scores [23], and anxiolytic effects were also observed in a more recent randomized, placebo-controlled (RCT) four-dose trial in patients with GAD [24].

CBD has also been studied in a recent RCT in social anxiety disorder, in which 57 healthy males received a single-dose of oral CBD (150, 300, or 600 mg) or placebo [25▪▪]. Following CBD administration, individuals completed a simulated public speaking test during which anxiety levels were assessed using a Subjective Visual Analogue Mood Scale. Compared to placebo, those who received 300 mg CBD 90 min prior to the public speaking task had significantly lower ratings of social anxiety ($P = 0.042$); whereas 150 and 600 mg CBD did not produce any detectable benefits. In a larger retrospective case series, adults with primary anxiety symptoms ($N = 72$) consumed 25 mg/day of CBD for 3 months [26▪]. One month following study initiation, 79.2% of patients reported experiencing improvements in symptoms as indicated by lower scored on the Hamilton Anxiety Rating Scale; this percentage remained relatively stable at three months. Although these results support a therapeutic effect of CBD in treating anxiety-related disorders, this study lacked a control condition. The authors also noted that patients in their clinic often expressed a desire to reduce or to avoid the use of psychiatric medications which may have exaggerated bias and a placebo effect as they received a desirable 'alternative' treatment [26▪].

Evidence for cannabis in anxiety can also be drawn from studies where it has been assessed as a secondary outcome, including two clinical trials investigating the efficacy of long-term use of cannabis or related compounds for other health conditions. A prospective open-label study assessed the effect of a cannabis herbal tea on pain-related symptoms, anxiety, and depression in patients ($N = 338$) with chronic pain for 12 months [27▪]. At the 3-month assessment point, patients reported significant improvements in anxiety as shown by a 3-point decrease the Hospital Anxiety and Depression Scale, which were maintained at endpoint. However, results differed in a recent pilot RCT of 18 patients with cannabis dependence. Patients who received either daily 2 mg nabilone or placebo for 10 weeks, did not produce significant between-group differences in anxiety symptoms at study endpoint from baseline, as measured by the Beck Anxiety Inventory [28].

CANNABIS AND ANXIETY: ONGOING STUDIES ON CLINICALTRIALS.GOV

Currently, two trials listed on ClinicalTrials.Gov directly investigate the relationship between cannabis use and anxiety. The first is a prospective study of changes in anxiety, negative affect, and inflammation following self-directed use of smoked cannabis flower and edibles [29]. Particularly, the study aims to understand differences between the anxiolytic effects of THC-based strains versus CBD-based strains versus strains that contain different ratios of THC and CBD (1 : 0, 1 : 1, or 0 : 1). The second trial assesses the efficacy of CBD oil for the treatment of several anxiety disorders, including Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, and agoraphobia. Participants will be randomized to receive CBD oil or placebo for an 8-week period and assessed based on the Hamilton Anxiety Rating Scale (HAM-A) [30].

Several other current studies indirectly assess the relationship between anxiety and cannabis use. One trial investigates the anesthetic potential of nabiximols in presurgery settings and assesses anxiety as a secondary outcome using self-assessed a visual analog scale [31]. Another trial assesses the effectiveness of cannabis oil in relieving cancer-related anxiety [32]. Finally, another open-label trial involves the use of a high CBD:low THC solution for the treatment of behavioral symptoms in older adults with Alzheimer's dementia, in which anxiety will be assessed with the Anxiety Domain on the Neuropsychiatric Inventory-Clinician scale and the GAD-7 [33].

SURVEY STUDIES

Despite a dearth of evidence and largely contradictory conclusions from empirical research, a substantial number of patients report using cannabis and related products to treat anxiety symptoms or disorders. In a pooled sample from 13 survey studies of cannabis use ($N = 6665$) 52% reported using cannabis for anxiety, making it the second-most commonly treated symptom, following pain [34▪▪]. These results reflect findings from the Australian 2016 Cannabis as Medicine Survey (CAMS-16; $N = 1748$), where 15% reported anxiety as the main medical condition treated with cannabis, and 51% reported using cannabis to treat anxiety symptoms [35▪]. Approximately 84% of users across all conditions described their symptoms as 'very much improved' or 'much improved' following cannabis use; whereas, a marginal proportion (less than 1%) of patients reported that cannabis exacerbated their symptoms, and only 1% experienced intolerable side effects.

Recent surveys have also assessed medical cannabis use in samples treating anxiety symptoms and disorders. In a survey of self-identified CBD users ($N = 2409$), 22.4% of respondents reported treating anxiety with CBD, making it the third-most commonly targeted symptom following chronic pain and joint pain [36▪]. Of the overall sample, almost 36% of respondents reported that CBD treated their medical conditions 'very well by itself', whereas only 4.3% reported 'not very well'. A survey study of 2032 medical cannabis users found that 43.7% of the sample used cannabis to treat anxiety symptoms [37▪]. Of those using for anxiety, most respondents (92%) felt that cannabis improved their anxiety symptoms despite symptoms remaining moderately severe (mean GAD-7 score 9.8 ± 5.5). Higher anxiety severity was associated with greater amounts of cannabis used daily ($P < 0.001$) and nearly half (49%) reported replacing a drug prescribed to them by their physician with medical cannabis. Antidepressants, followed by opioids and benzodiazepines, were the most frequent drugs replaced by cannabis. Of note, 99% of this sample had used cannabis recreationally prior to their medicinal cannabis use [37▪]. A similar finding was reported from a sample of 2774 patients who use cannabis to treat various medical conditions: 58% substituted prescription medications with cannabis [38]. Specifically, 13.6% of patients substituted anxiolytic and benzodiazepine medications with medical cannabis, making these medications the second-most substituted drug class following narcotics/opioids (35.8%). In further support of these results, a survey of dispensary members ($N = 1513$) conducted by Piper *et al.* [39] revealed that 71.8% of respondents reduced their intake of antianxiety medications.

The Strainprint Cannabis Tracker is a smartphone application designed for medical cannabis users to track symptom changes as a function of cannabis use (dose and THC:CBD ratio can be tracked) [40▪▪]. A sample of 5085 tracking sessions collected by the app, in which patients used cannabis to alleviate anxiety, were analyzed. Results were very positive, as users of the app reported significantly lower anxiety levels following cannabis use in 93.5% of sessions analyzed; only 2.1% experienced exacerbated symptoms, whereas 4.4% experienced no symptom change. With regards to THC:CBD ratio, patients perceived the largest stress reductions from high CBD cannabis products [40▪▪].

Only one survey has investigated the long-term effects of cannabis on anxiety in a 3-year longitudinal survey of cannabis use in patients with a primary anxiety disorder diagnosis ($N = 3723$) [41▪]. Between-group measures of remission rates and other mental health measures were compared among cannabis users, individuals with cannabis use disorder (CUD), and nonusers. Remission rates

from anxiety disorders were higher among cannabis nonusers (66.0%) compared to cannabis users (52.8%), and were lowest among individuals with CUD (46.8%), however these differences were not statistically significant in adjusted models. Notably, 43% of those who reported long-term cannabis use qualified for a CUD diagnosis. Contrary to the majority of surveys reviewed, these results suggest that long-term cannabis use neither harms nor improves the course of anxiety disorders, but may increase risk of disordered use [41▪].

RISKS OF CANNABIS USE: DEPENDENCE AND ANXIETY

Excessive cannabis use may result in the development of CUD, which includes symptoms related to cannabis dependence and other associated problems. Recent data show treatment demand for cannabis problems to have increased by 76% between 2006 and 2016 in 25 European countries, which suggests that CUDs are on the rise [5▪]. Medical cannabis use has been identified as a prominent risk factor, as medical cannabis users demonstrate elevated rates of CUD [42▪,43]. This raises the question of whether cannabis dependence affects susceptibility and other associations with anxiety disorders. A recent review suggests that higher cannabis use, especially at a level of disordered use, is associated with a higher risk of anxiety [5▪]. Evidence from the National Comorbidity Survey [2] suggested that subjects with cannabis dependence were twice as likely to be diagnosed with an anxiety or mood disorder; specifically, the comorbidity between cannabis dependence and anxiety disorders ranged from 6.9% to 29%, which is higher than those without cannabis dependence. In a separate large-scale Australian survey, cannabis use was found to be unrelated to anxiety after adjusting for demographic characteristics, other substance use, and personality traits [44]. Furthermore, Agosti *et al.* [45] reported a considerable number of patients to have developed anxiety disorders prior to the onset of cannabis dependence symptoms, suggesting that some of patients may have self-prescribed cannabis to treat their anxiety. In support of this, Buckner *et al.* [46] found social anxiety to be an independent risk factor for cannabis dependence. As such, Manthey [5▪] suggests that a causal relationship between cannabis use and long-term anxiety disorders is unlikely, given contradictory evidence from various studies. Other risk factors for cannabis dependence include the use of other substances, including tobacco, male sex, high stress, high impulsivity, and low self-esteem [43,47,48]. Older age at diagnosis has also been identified as a risk factor as has earlier age of cannabis use initiation [43].

Investigations have also been conducted on the association between cannabis and specific manifestations of anxiety, including panic attacks. Although no recent studies have been published, previous survey studies have suggested a positive relationship between cannabis use and panic attacks/panic disorder [49,50]. Cannabis use has been significantly associated with an increased odds of lifetime panic attack history, and lifetime and past-year diagnosis of panic disorder [49]. In addition, a prospective adolescent study found that cannabis use and dependence were significantly associated with increased odds of developing panic attacks and panic disorder [51]. Cannabis has also long been associated with inducing panic attacks [52,53▪▪]. Some researchers have hypothesized that there may be mechanistic differences between ordinary panic attacks and those induced by cannabis; in particular that the function of the hypothalamics–pituitary–adrenal (HPA) axis may differ between panic disorder and cannabis-induced panic attacks [53▪▪]. This hypothesis remains under examination.

CONCLUSION

The research surrounding the treatment of anxiety with cannabis is emerging, but is not yet at a stage where any strong conclusions may be drawn. Studies of animal models are promising, signaling an anxiolytic ability of CBD, THC, and other CB1R agonists; however, the mechanisms behind these effects remain equivocal. This mixed literature may be the consequence of variability in critical factors including when and how treatment is administered, dosing, and duration of treatment. These limitations also extend to the oblique evidence drawn from the existing clinical literature, which is routinely criticized by reviews for the high risk of bias and small sample sizes [18▪,19▪,20▪], as inadequately powered studies may result in exaggerated significance in treatment effects or lack thereof. Further, results based on nonclinical subjects, or single-dose studies provide oblique evidence, at best, for the therapeutic nature of cannabis for anxiety. The samples that have been examined, either clinical or nonclinical have not been well characterized. These samples may contain individuals who have clinical characteristics and comorbidities that make them less responsive to treatment and therefore may obfuscate the actual treatment effect. In addition, studies of anxiety among other clinical populations may not be generalizable to clinically anxious groups. More specifically, these studies are unable to preclude improvements in anxiety are not simply a consequence of improved

symptoms of their primary condition. Results of survey studies generally suggest strong subjectivity in the reported anxiolytic effects of cannabis as these studies include samples of cannabis users, who have likely had largely positive experiences with medical cannabis [36▪]. Whether these effects hold true in empirical trials has yet to be verified.

Despite the equivocal nature of the literature regarding cannabis' ability as an anxiolytic, survey outcomes suggest that many patients are embracing cannabis as a treatment for their anxiety, which may warrant a more thorough evaluation of this alternative treatment. The landscape of cannabis legalization is rapidly evolving and cannabis is more easily accessible than ever before. It is anticipated that cannabis use in the general population will increase exponentially as more and more jurisdictions allow its use. Further research is critical to reconciling discrepancies between survey outcomes and results from clinical trials so that patients and clinicians can make informed decisions regarding treating their anxiety with cannabis.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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