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REVIEW

Is cannabis treatment for anxiety, mood, and related disorders ready for prime time?

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Anxiety and related disorders are the most common mental conditions affecting the North American population. Despite their established efficacy, first-line antidepressant treatments are associated with significant side effects, leading many afflicted individuals to seek alternative treatments. Cannabis is commonly viewed as a natural alternative for a variety of medical and mental health conditions. Currently, anxiety ranks among the top five medical symptoms for which North Americans report using medical marijuana. However, upon careful review of the extant treatment literature, the anxiolytic effects of cannabis in clinical populations are surprisingly not well-documented. The effects of cannabis on anxiety and mood symptoms have been examined in healthy populations and in several small studies of synthetic cannabinoid agents but there are currently no studies which have examined the effects of the cannabis plant on anxiety and related disorders. In light of the rapidly shifting landscape regarding the legalization of cannabis for medical and recreational purposes, it is important to highlight the significant disconnect between the scientific literature, public opinion, and related policies. The aim of this article is to provide a comprehensive review of the current cannabis treatment literature, and to identify the potential for cannabis to be used as a therapeutic intervention for anxiety, mood, and related disorders. Searches of five electronic databases were conducted (PubMed, MEDLINE, Web of Science, PsychINFO, and Google Scholar), with the most recent in February 2017. The effects of cannabis on healthy populations and clinical psychiatric samples will be discussed, focusing primarily on anxiety and mood disorders.

KEYWORDS
anxiety disorders, cannabis treatment, depression, endocannabinoids, marijuana

1 | INTRODUCTION

Cannabis, a derivative of the *Cannabis sativa* plant, is the most commonly used illicit drug with 2.5% of the world population reporting consumption on an annual basis (World Health Organization, 2016). It is commonly used recreationally for its euphoric and relaxing effects. The dried plant is typically smoked or vaporized, but can also be consumed in foods or used as a concentrated oil. Despite its designation as an illicit substance in many parts of the world, regulatory bodies in the Netherlands, and several states in the United States have legalized its use for recreational purposes. Canada is also moving toward legalization of recreational cannabis in 2018.

Cannabis has been used for millennia for its purported therapeutic properties, leading to exploration of its active constituents, the cannabinoids. Although there are over 400 known compounds in the cannabis plant (D'Souza & Ranganathan, 2015), the effects of cannabis have mainly been explored in terms of the cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

1.1 | Δ^9-Tetrahydrocannabinol

Known as the main psychoactive component of cannabis, THC exerts its effects through the endocannabinoid system, by acting on two G-protein coupled receptors: cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) receptors. THC is a partial agonist of CB_1 receptors, which are expressed throughout the body, but principally function presynaptically in the central nervous system. CB_2 receptors are thought to be linked to immune function and are concentrated in peripheral tissues (Pacher, Bátkai, & Kunos, 2006). Under specific conditions and at particular doses, THC has been shown to have anxiolytic, antidepressant and hypnotic effects in patients suffering from cancer (Regelson et al., 1976), multiple sclerosis (MS) (Martyn, Illis, & Thom, 1995; Wade, Robson, House, Makela, & Aram, 2003), and in healthy subjects

(Ashton, Golding, Marsh, Millman, & Thompson, 1981). Although at higher doses THC has demonstrated the opposite effect, inducing panic, paranoia and anxiety in subjects (D'Souza et al., 2004; Fusar-Poli et al., 2009). Chronic exposure to THC can also be neurotoxic; a point of concern as the THC:CBD ratio in "street" cannabis has significantly increased compared to previous decades (Swift, Wong, Li, Arnold, & McGregor, 2013).

1.2 | Cannabidiol

CBD is a phytocannabinoid constituent of cannabis which lacks the significant psychoactive, or "high-inducing," effects of THC but has demonstrated anti-inflammatory, analgesic, anticonvulsant, and anxiolytic properties (Blessing, Steenkamp, Manzanares, & Marmar, 2015). Although the mechanism behind these effects remains unclear, the function of CBD may be related to its action as an antagonist/inverse agonist of CB_1 receptors (Thomas et al., 2007) or as a positive allosteric modulator of $5HT_{1A}$ receptors (Rock et al., 2012). When administered together, CBD may also have the ability to reverse the unwanted and anxiogenic effects of THC by antagonizing THC pharmacodynamically (Bhattacharyya et al., 2010; Fusar-Poli et al., 2010; Zuardi, 2008; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982).

1.3 | Synthetic compounds

Cannabinoid research has also extended to the development and testing of synthetic cannabinoids including dronabinol, nabilone, and Sativex. Although dronabinol is a pure (−)-*trans*-isomer of THC, it is a complete agonist of CB_1 receptors; consequently, the effect of dronabinol outlasts and has a slower onset than THC (Cooper, Comer, & Haney, 2013). It is currently approved for use in refractory nausea and vomiting in cancer as well as loss of appetite and cachexia (wasting syndrome) in HIV/AIDS (Grotenhermen, 2003). Similarly, nabilone, another synthetic derivative of THC, is also an agonist of the endocannabinoid system. It is currently approved for nausea and vomiting associated with cancer chemotherapy (Grotenhermen, 2003). Sativex is an extract of chemically and genetically characterized *Cannabis sativa* plants. The principal active components in Sativex are THC and CBD (Health Canada, 2005). It is available in the form of a buccal spray and is primarily used for treatment of neuropathic pain in MS.

1.4 | Cannabinoids as therapeutic interventions

Cannabis, in the form of medical marijuana, is currently being used as a therapeutic intervention for a myriad of medical and psychiatric problems. However, the meta-analytic evidence supporting such claims is limited to a few conditions including chronic pain (Martín-Sánchez, Furukawa, Taylor, & Martin, 2009), neuropathic pain (Iskedjian, Bereza, Gordon, Piwko, & Einarson, 2007; Phillips, Cherry, Cox, Marshall, & Rice, 2010), and nausea (Machado Rocha, Stefano, De Cassia Haiek, Rosa Oliveira, & Da Silveira, 2008). These meta-analyses include studies of smoked or vaporized cannabis and synthetic cannabinoids. At present time, cancer, HIV/AIDS, MS, and chronic pain, rank among conditions which receive the most frequent approval for medical marijuana in Canada and the United States (Health Canada, 2016; D'Souza 2016). In some instances, authorization to use medical marijuana has also been extended to psychiatric conditions such as posttraumatic stress disorder (PTSD) and Tourette's Syndrome (TS), with a recent systematic review suggesting preliminary evidence for PTSD (Walsh et al., 2017).

Mental illness affects approximately one in five individuals in the United States and Canada, with anxiety disorders ranked as the most prevalent (Center for Behavioral Health Statistics and Quality, 2015; Public Health Agency of Canada, 2012). Anxiety disorders are chronic conditions and include panic disorder (PD), agoraphobia, social anxiety disorder (SAD), generalized anxiety disorder (GAD), and specific phobias with a combined lifetime prevalence of 29% (Kessler et al., 2005). Anxiety disorders are associated with significant burden for afflicted individuals, their families and society, and frequently co-occur with other psychiatric problems including major depressive disorder (MDD), bipolar disorder (BD), PTSD, obsessive-compulsive disorder (OCD) as well as trichotillomania (TTM) and TS.

First-line pharmacological treatments for anxiety disorders and most of their comorbid conditions (except BD, TTM, and TS) include antidepressants. Unfortunately, treatment response rates to these standard agents are less than optimal, with 40–60% of patients continuing to have residual, impairing symptoms (Bandelow et al., 2008). These treatments are also associated with significant, often disabling side effects leading to noncompliance and discontinuation (Olfson, Marcus, Tedeschi, & Wan, 2006). Cognitive-behavioral therapy is the first-line psychological treatment for anxiety disorders and yields response rates of 46–77% (Katzman et al., 2014). Unfortunately, this treatment is not widely available and is often associated with significant cost to the patient (Katzman et al., 2014).

Large proportions of regular cannabis users also suffer from anxiety disorders (Cheung et al., 2010), with some suggesting symptom improvement following cannabis use. The observational and epidemiological literature appears to associate cannabis use with mental health risks rather than benefits, including risks of psychosis and worsening of anxiety symptoms (National Academy of Sciences, Engineering and Medicine, 2017). Further, the majority of the current prospective treatment literature is based on synthetic cannabinoids and pure THC or CBD rather than the cannabis plant. Nevertheless, cannabis continues to be used in the community as an anxiolytic. The purpose of this review is to examine the available treatment literature in terms of the efficacy and risks associated with cannabinoid treatment of anxiety and related disorders.

1.5 | SEARCH METHOD

To develop a comprehensive review evaluating cannabis and related compounds on symptoms of various psychiatric conditions, searches of five electronic databases were conducted (PubMed, MEDLINE, Web of Science, PsychINFO, and Google Scholar), with the most recent in February 2017. Search terms included combinations of "cannabis," "THC," "cannabidiol," "endocannabinoid," "sativex," "dronabinol," nabilone," "anxiety," "depression," "bipolar," "social

anxiety disorder," "panic disorder," "post-traumatic stress," "obsessive-compulsive," "Tourette's," and "trichotillomania," Given the limited published literature examining the effects of cannabis in the relevant clinical populations, data on all available trials (from published peer-reviewed journals or conference abstracts) are included.

2 | EFFECTS OF CANNABINOIDS ON ANXIETY: HEALTHY POPULATIONS

Although anxiety and mood problems are not commonly recognized by governing bodies as valid health conditions to receive medical marijuana, approximately 4% of Canadians report using marijuana for medical conditions including anxiety. In both Canada and the United States, anxiety also ranks among the top five conditions that individuals are treating with medical marijuana (Reinarman, Nunberg, Lanthier, & Heddleston, 2011; Walsh et al., 2013). Stress relief and relaxation are frequently reported as drivers of cannabis use (Bonn-Miller et al., 2007); with chronic healthy users typically reporting lower levels of anxiety than noncannabis using controls shortly after cannabis use (Sethi et al., 1986). There are also many anecdotal reports purporting the anxiolytic nature of cannabis. However, the evidence supporting this notion is limited to single-dose studies in nonclinical, healthy samples. Despite these claims of cannabis users, there are no published prospective studies evaluating the anxiolytic effects of cannabis in its most frequently used forms (smoked or vaporized), albeit other compounds with abilities to modulate the endocannabinoid system have been evaluated and comprise much of the relevant body of literature.

2.1 | Δ^9-Tetrahydrocannabinol

THC has demonstrated biphasic, dose-dependent effects to both induce (10 mg) and decrease (1.25–30 mg) levels of anxiety in healthy adults (Bhattacharyya et al., 2010; Bossong et al., 2013; Fusar-Poli et al., 2009; Karniol, Shirakawa, Kasinski, Pfeferman, & Carlini, 1974; Martin-Santos et al., 2012). At specific doses, neuroimaging data have also demonstrated that THC can both increase (Fusar-Poli et al., 2010) and decrease (Bossong et al., 2013) emotional arousal/processing of negative stimuli.

2.2 | Cannabidiol

Unlike THC, CBD has repeatedly demonstrated an anxiolytic ability and successfully abolished the anxiogenic effects of THC (Bhattacharyya et al., 2010; Fusar-Poli et al., 2009; Karniol et al., 1974; Zuardi et al., 1982). For example, CBD (300 mg) has been shown to have the same poststress anxiolytic effects as isapirone (5 mg), a selective 5-HT_{1A} receptor partial agonist (Zuardi, Cosme, Graeff, & Guimaraes, 1993). Healthy participants have also reported decreased levels of subjective anxiety, 90-min postadministration of 400 mg CBD. This anxiolytic basis of CBD is further supported by neuroimaging studies associating CBD administration (vs. placebo and/or THC) with decreased activity in limbic and paralimbic regions during emotional face processing tasks (Crippa et al., 2004; Fusar-Poli et al., 2010). CBD (32 mg) has also been shown to enhance consolidation of extinction learning in healthy humans (Das et al., 2013).

2.3 | Synthetic cannabinoids

Dronabinol has also been studied in healthy populations. A crossover, double-blind randomized controlled trial (RCT) ($n = 16$) showed dronabinol (7.5 mg) administration reduced limbic (right lateral amygdala) reactivity to angry or fearful faces during an emotional faces processing task (Phan et al., 2008). Dronabinol has also been used to evaluate the effects of cannabinoids on fear extinction, a key component of PTSD and anxiety disorders (Rauch, Shin, & Phelps, 2006). Enhancing endogenous cannabinoids has been shown to facilitate fear extinction in rats (Chhatwal, Davis, Maguschak, & Ressler, 2005), and the translation of such findings to humans has recently become of interest. Rabinak et al. (2013) combined a standard Pavlovian fear conditioning and extinction paradigm with dronabinol (7.5 mg) or placebo 2 hr prior to extinction learning in healthy individuals ($n = 29$). They tested extinction retention 24 hr later revealing that oral administration of dronabinol in healthy individuals prior to the extinction of a learned fear response was found to facilitate fear extinction (Rabinak et al., 2013). Moreover, fMRI-imaging data has related this enhanced rate of extinction to increased ventromedial prefrontal cortex and hippocampal activity to a previously extinguished conditioned stimulus (Rabinak et al., 2014).

3 | EFFECTS OF CANNABINOIDS ON ANXIETY, MOOD, AND RELATED DISORDERS

Research involving clinically anxious populations began with an early study by Fabre and McLenden (1981) who evaluated the effects of the synthetic cannabinoid, nabilone, in psychoneurotic anxiety in both an open-label ($n = 5$) and double-blind study ($n = 20$). The open-label trial (mean dose = 2.8 mg, range = 2–8 mg/day) presented significant reductions in anxiety as per the Hamilton Anxiety Rating Scale (HAM-A) ($P < .001$). In the double-blind, fixed-dose study, nabilone (3 mg/day, 1 mg t.i.d) was found to be superior to placebo ($n = 20$) as per the HAM-A ($P < .001$) and Physician's Global Impression ($P = .002$) by Day 7 (Fabre & McLenden, 1981). More recently nabilone was associated with a 26.5% improvement in "generalized anxiety scores" in a small study of patients also taking an antidepressant medication for mixed anxiety and mood disorders (Lee, 2009). With respect to individual anxiety disorders, only CBD has been evaluated in two small SAD studies and nabilone has been evaluated in GAD.

3.1 | Social anxiety disorder (SAD)

3.1.1 | Cannabidiol

In a double-blind RCT, 24 drug-naïve SAD patients were given a single-dose of 600 mg of CBD (SAD-CBD) (powder dissolved in corn oil, capsule) or placebo (SAD-placebo) 1.5 h prior to a simulated public speaking task (Bergamaschi et al., 2011). Alterations in state anxiety,

sedation, cognitive impairment and discomfort were measured using subjective ratings of the respective Visual Analogue Mood Scale (VAMS), a scale where the subject is told to mark a point that identifies his/her present subjective state on a 100 mm straight line placed between two words that describe opposite mood states. During the speech phase, the SAD-CBD group presented less subjective anxiety than both the SAD-placebo group ($P = .012$) and healthy controls ($P = .007$) as per the VAMS anxiety factor. Pretreatment with CBD also significantly reduced cognitive impairment and discomfort in their speech performance than in the SAD-placebo group based on the VAMS. As per the negative self-evaluation subscale, CBD intake almost abolished the increased negative self-evaluation during the speech phase (SAD-placebo vs SAD-CBD, p = .001). The observed power used in the statistical analysis of the anxiety VAMS factor and in the negative self-evaluation scale were 0.996 and 0.881, respectively (Bergamaschi et al., 2011).

Similarly, reduced levels of subjective anxiety were observed in a small trial of 10 SAD men following ingestion of a 400 mg CBD capsule, as compared to placebo (Crippa et al., 2011). With the primary purpose of evaluating the neurophysiological effects of CBD in SAD using neuroimaging, the anxiety-evoking stimulus in this study was the scanning process itself. CBD intake was associated with decreased VAMS anxiety scores at phases of venous cannula insertion ($P < .02$), preimaging ($P < .006$), and postimaging ($P < .003$) (Crippa et al., 2011). However, it should be noted that given the SAD population, the scanning process was not a well-suited anxiety-provoking stimulus. Finally, neither study used objective or clinician-rated measures of anxiety further limiting conclusions drawn from these study methodologies.

3.2 | Generalized anxiety disorder (GAD)

3.2.1 | Synthetic cannabinoids

The effect of a single dose of nabilone was evaluated in individuals diagnosed with either anxiety neuroses or GAD in a Phase I ($N = 4$) and a Phase II study ($N = 4$) (Glass, Uhlenhuth, Hartel, Schuster, & Fischman, 1981). In both phases, participants were administered placebo or nabilone (1–5 mg—Phase I; 1–4 mg—Phase II) over four sessions, each 7 days apart. Anti-anxiety effects were only noted in two of four patients, at doses of 1–2 mg in Phase I. Lower doses were utilized in Phase II due to the adverse events observed in Phase I and no antianxiety effects were observed (Glass et al., 1981). Similarly, Ilaria et al. (1981) also found 2–5 mg/day of nabilone to reduce symptoms of anxiety neurosis in a placebo-controlled crossover trial. Although these findings may show promise, these studies utilized DSM-III criteria which may potentially limit their applicability to current disordered populations.

3.3 | Major depressive disorder

Aside from its anxiolytic abilities, cannabis has also been thought to induce a sense of euphoria. It has been reported that many people begin cannabis use during depressive episodes (Feingold, Weiser, Rehm, & Lev-Ran, 2015). Studies have also suggested that MDD can also occur with alterations in the endocannabinoid system (Aso, Ozaita, Serra, & Maldonado, 2011; Gorzalka & Hill, 2011; Mechoulam & Parker, 2013) and preclinical studies show that genetic deletion of CB_1 receptors results in depressive-like behaviors (Aso et al., 2011; Valverde & Torrens, 2012).

3.3.1 | Plant based

Improvements in depressive symptoms have been described in five case reports of individuals with a history of cannabis use, where an antidepressant effect extended beyond that of acute intoxication. Four of five patients reported that the efficacy of cannabis superseded the benefits of past treatment trials of antidepressants. However, these findings were limited by retrospective reports and all cases fulfilled DSM-IV criteria for cannabis or polysubstance abuse (Gruber, Pope, & Brown, 1996).

3.3.2 | Δ^9-tetrahydrocannabinol

In a double-blind, placebo-controlled trial, THC (0.3 mg/kg twice a day for 7 days) failed to show significant euphoria or an antidepressant effect in eight hospitalized depressed patients (Kotin, Post, & Goodwin, 1973), whereas a second double-blind study described THC to actually induce dysphoria in the study sample (Ablon & Goodwin, 1974).

3.3.3 | Synthetic cannabinoids

Two case reports have used dronabinol (5–7.5 mg) either adjunctively or as monotherapy in patients with recurrent depressive episodes. Improvement in quality of life, mood stability, and severity of mood and comorbid conditions were reported (Blass, 2008).

Synhexyl (parahexyl) is a synthetic homologue of THC that was made illegal in the early 1980s after being classified as a Schedule I compound with no medical use. Although it has demonstrated an ability to alleviate depressive mental states (Stockings, 1947), the amphetamine, benzedrine was deemed superior to synhexyl in an open-label study (Pond, 1948).

3.4 | Bipolar disorder

There is evidence suggesting that manic symptoms may exacerbate following cannabis use in individuals with BD (Gibbs et al., 2015). Meta-analytic evidence has also suggested that cannabis use may be associated with an increased risk for onset of new manic symptoms (OR: 2.97; 95% CI: 1.80–4.90) (Gibbs et al., 2015). Yet, anecdotal reports suggest that some patients use marijuana to relieve both depressive and manic symptoms (Gruber et al., 1996; Henquet, Krabbendam, de Graaf, ten Have, & van Os, 2006)

3.4.1 | Plant based

An observational study evaluated the effects of cannabis on mood in users with BD (MJBD, $n = 12$) compared to users without BD (MJ, $n = 20$; no Axis I pathology) and nonusing BD patients ($n = 11$) (Gruber et al., 2012). Participants completed three daily ratings, 4 days/week on a Palm Pilot customized with the HAM-A, Young Mania Rating Scale (YMRS), Profile of Mood Scales (POMS), and Montgomery Asberg Depression Rating Scale (MADRS). Following cannabis use,

MJBD patients reported lower HAM-A ($P < .01$) and MADRS scores ($P < .005$) and several measures of the POMS compared to the MJ group. However, when compared to nonusing BD patients, the MJBD group reported worse scores on the MADRS ($p < .001$) and YMRS ($p < .001$), but also reported improvements as per certain POMS subscales (confusion ($P < .001$), tension ($P < .001$), and fatigue ($P < .005$)) after smoking cannabis (Gruber et al., 2012).

3.4.2 | Cannabidiol

The effect of CBD in BD has been discussed in two case reports (Zuardi et al., 2010). From day 6 to 30, one inpatient received CBD twice daily (initial dose 600 mg/day increased to 1200 mg/day) with adjunctive olanzapine (10–15 mg/day, discontinued at day 20). On day 31, CBD treatment was replaced with placebo for 5 days. The same treatment plan was followed for the second case, omitting adjunctive olanzapine. Although both patients tolerated CBD well, observed improvements were limited to the first case (taking CBD and olanzapine) with reductions of 37 and 33% in the YMRS and Brief Psychiatric Rating Scale (BPRS), respectively (Zuardi et al., 2010).

3.5 | Posttraumatic stress disorder

The therapeutic benefits of cannabis for PTSD symptomology are mechanistically supported by the role of the CB_1 receptors in fear acquisition, a process central to PTSD. For instance, the glucocorticoid hormone facilitated hyperconsolidation of traumatic memories is mediated by CB_1 receptors (Campolongo et al., 2009; Hill & McEwan 2009). Furthermore, PET imaging has characterized PTSD patients with elevated CB_1 receptor availability and decreased anandamide concentrations in the amygdala-hippocampal-corticostriatal circuitry (Neumeister et al., 2013) implicated in PTSD. These preclinical findings along with substantial bodies of animal work implicate a role of the endocannabinoid system in PTSD.

There are documented reports of cannabis use to treat PTSD symptoms of anxiety and insomnia (Bonn-Miller, Babson, & Vandrey, 2014; Grant, Pedersen, & Neighbors, 2016). Lifetime and current PTSD diagnosis has also been associated with increased odds of cannabis use and daily use in the past year in adults (Cougle, Bonn-Miller, Vujanovic, Zvolensky, & Hawkins, 2011; Kevorkian et al., 2015), although use in adolescents with PTSD is also very common (Lipschitz et al., 2003). Retrospective studies have presented mixed results. In one study, severity scores on the Clinician-Administered PTSD Scale (CAPS) were lower for cannabis users than nonusers (Greer, Grob, & Halberstadt, 2014); whereas another report indicated no differences in PTSD Checklist – Civilian Version (PCL-C) scores (Johnson et al., 2016). A recent longitudinal observational study also reported worse PTSD symptoms in patients who continued to use marijuana after being discharged when compared to those who stopped and those who had never used (Wilkinson, Stefanovics, & Rosenheck, 2015). Cannabis can currently be prescribed in nine U.S. states to help with symptoms of PTSD, however the body of clinical work is limited to a small number of trials discussed below.

3.5.1 | Plant based

Reznik (2011) evaluated the effects of smoked cannabis in a population of PTSD patients who applied for a medical marijuana license ($n = 160$). They followed those who were approved for a license (approximately 50% of sample) in an observational study for 2 years. Improvements in the Quality of Life Scale, pain scores, and the CAPS were reported "in most cases" with 2–3 mg/day of smoked cannabis. Another unpublished open-label study, evaluated the effects of adjunctive smoked cannabis (ad lib, approximately 23% THC, <1% CBD, maximum 100 mg/month), over 16, 28, and 44 weeks in 29 Israeli male combat Veterans with PTSD. A significant decrease in CAPS total score was noted from baseline to first follow-up (4.3 months later, $n = 26$), second follow-up 7.6 months later ($n = 25$), and final follow-up at approximately 11.3 months ($n = 10$) (Mashiah, 2012). Given that these findings have not been published, information regarding statistical analyses was not available. In addition, a published case report of a patient with significant anxiety, dissociation, and flashbacks related to PTSD symptoms also reported finding his symptoms to be more manageable with cannabis use (Passie, Emrich, Karst, Brandt, & Halpern, 2012).

3.5.2 | Δ^9-Tetrahydrocannabinol

The effects of adjunctive THC in a 3-week, open-label, adjustable dose trial in chronic PTSD ($n = 10$) have also been evaluated (Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014). Patients were given 100 mg of THC dissolved in 4 ml of olive oil and instructed to take 0.1 ml (equivalent of 2.5 mg) beneath their tongue 1 hr after waking and 2 hr before bedtime. If tolerated, the dose was increased to 0.2 ml (equivalent of 5 mg). Statistically significant changes posttreatment included decreased PTSD hyperarousal symptoms (based on the CAPS) ($P < .02$), Clinical Global Impression – Improvement (CGI-I) ($P < .03$) and Clinical Global Impression – Severity (CGI-S) ($P < .02$), sleep quality, frequency of nightmares ($P < .04$), and Nightmare Effects Survey score ($P < .002$). Moreover, two patients noted complete remission of their nightmares at posttreatment. However, CAPS total, intrusion and avoidance scores did not improve pre- to posttreatment (Roitman et al., 2014).

3.5.3 | Synthetic cannabinoids

A retrospective chart review ($n = 104$) of nabilone treatment (mean final dose = 4.0 mg, range 0.5–6.0 mg) over 11.2 weeks (mean length of treatment, range 1 day to 36 weeks) for PTSD, revealed significant decreases in PCL-C scores (38.8 [SD, 7.1]; $t57 = 10.2$, $P = .001$) and the Global Assessment of Functioning posttreatment: mean, 58.2 (SD, 8.4); $t100 = 16.9$, ($P = .001$), from pre- to posttreatment. Subjects also reported significantly increased number of hours slept ($P < .001$) and decreased frequency of nightmares ($p<.001$) (Cameron, Watson, & Robinson, 2014). Similarly, adjunctive nabilone has also shown cessation or significant reduction of nightmares based on subjective reports of nightmare presence and ratings of intensity in 72% of a sample of 47 individuals with PTSD (Fraser, 2009). Most experienced a recurrence of nightmares when nabilone was discontinued, but responded once reinitiated (Fraser, 2009).

More recently, a 16-week, cross-over RCT ($N = 10$) with nabilone (1.95 ± 0.9 mg/day) revealed promising results (Jetly, Heber, Fraser, & Boisvert, 2015). In addition to being well-tolerated, a significant reduction in nightmares, as measured by the CAPS Recurring and Distressing Dream score (primary efficacy measure), was noted ($P = .03$). CGI-I was also lower in the nabilone-treated group ($P < .05$) and scores on the general wellbeing questionnaire were significantly improved ($P = .04$). However, no effect was observed on sleep quality or quantity as measured by the CAPS falling and staying asleep items, or the Sleep Diary (Jetly et al., 2015).

3.6 | Obsessive-compulsive disorder (OCD)

The endocannabinoid system presents an attractive target for the treatment of OCD, as preclinical rodent studies have demonstrated that CBD and synthetic CB_1 receptor agonists reduce marble burying behavior, whereas pretreatment with CB_1 receptor antagonists inhibit this effect (Casarotto, Gomes, Resstel, & Guimarães, 2010; Gomes, Casarotto, Resstel, & Guimarães, 2011). Moreover, the effects of CBD have been linked to 5-HT_{1A} receptor activity (Rock et al., 2012) and serotonergic dysfunction is implicated in the pathophysiology of OCD (Wu, Hanna, Rosenberg, & Arnold, 2012). There is also an abundance of CB_1 receptors in the striatum, a component of the corticostriatal-thalamocortical circuit which is believed to be dysfunctional in OCD (Schindler, Anghelescu, Regen, & Jockers-Scherubl, 2008; Wu et al., 2012). Many synapses in this region are also glutamatergic. Since glutamate hyperactivity is believed to be one mechanism that underlies OCD symptomology (Wu et al., 2012), and cannabinoids inhibit glutamate release in the central nervous system (Gomes et al., 2011), the endocannabinoid system may be a novel target for OCD research.

3.6.1 | Synthetic cannabinoids

There is one report describing the effect of adjunctive dronabinol (20–30 mg/day), in two refractory cases of OCD with comorbid MDD or schizophrenia (Schindler et al., 2008). Significant symptom improvement was observed after 10–14 days as per the Yale Brown Obsessive Compulsive Scale (Y-BOCS) in both cases.

3.7 | Trichotillomania

3.7.1 | Synthetic cannabinoids

In a 12-week, open-label study of flexibly dosed dronabinol (mean effective dose of 11.6 ± 4.1 mg/day), 64.3% of 14 female patients with trichotillomania responded to treatment (≥35% reduction on the Massachusetts General Hospital Hair Pulling Scale and CGI-I score of 1 or 2) (Grant, Odlaug, Chamberlain, & Kim, 2011).

3.8 | Tourette's syndrome (TS)

The effects of cannabis on other conditions involving repetitive behaviors, such as tic disorder and TS have also been evaluated. One possible hypothesis, exclusive of the dopaminergic system, could be that CB_1 receptor agonists may inhibit the excitatory inputs into the basal ganglia, by inhibiting glutamate release, therefore reducing motor activity (Grant et al., 2011; Schindler et al. 2008).

3.8.1 | Plant based

In tic disorder, anecdotal and case reports have suggested that smoked cannabis (1–2 joints/day) can result in decreased urge to tic and intensity of tics (Sandyck & Awerbuch, 1988) or complete cessation of tics (Hemming & Yellowlees, 1993). Similarly, a retrospective study reported that 82% of subjects reported marked improvement in both motor and vocal tics (Müller-Vahl, Kolbe, Schneider, & Emrich, 1998).

3.8.2 | Δ^9-Tetrahydrocannabinol

In addition to a case report (Muller-Vahl, Schneider, Kolbe, & Enrich, 1999), Müller-Vahl et al. (2002) conducted a cross-over, RCT investigating the effects of a single dose of 5 mg ($n = 4$), 7.5 mg ($n = 6$), or 10 mg ($n = 2$) of THC (in gelatin capsules) or matching pill placebo. Following a single dose of THC, significant improvements over placebo were limited to the patient-reported tic severity measure, the Tourette's Syndrome Symptom List ($P = .015$). This was followed by a 6-week RCT of 24 TS patients taking 2.5–10 mg/day of THC, where a significant reduction in tic severity and motor tic intensity on the Tourette's Syndrome Global Impressions Scale was found compared to placebo ($P = .008$ and .05, respectively) (Müller-Vahl et al., 2003).

4 | RISKS ASSOCIATED WITH CANNABIS USE

Despite the limited literature, it appears that the constituents of cannabis and synthetic cannabinoids may have the potential to modify levels of anxiety. At the same time, cannabis has also been associated with adverse events including increased anxiety, psychosis, neurocognitive impairment, and addiction, which presents significant limitations to its use as a treatment. For instance, feelings of anxiety and panic often consequent to cannabis use, have been reported to drive the high rates of hospital emergency room visits in users (Crippa et al., 2009). Unfortunately, neither the compound, nor users have been characterized well enough to determine who will have an anxiogenic versus anxiolytic response following use. Another frequently cited concern with cannabis use relates to the increased risk of psychosis in those with a preexisting genetic vulnerability to schizophrenia, particularly with regular cannabis use (Ksir & Hart, 2016; Volkow, Baler, Compton, & Weiss, 2014). This is supported by the recent review published by the National Academy of Sciences, Engineering and Medicine (2017) discussing both the effects of cannabis use on the risk of developing a given disorder and also its effects on the symptoms or course of a disorder in patients with a given condition. Although cannabis use was not associated with an increased risk for developing depression, anxiety, or PTSD, it was associated with a substantial risk for the development schizophrenia or psychoses. Similarly, there was moderate evidence of a statistical association between regular cannabis use and incidence of SAD and suicidal ideation, attempts and completions. There was also limited evidence to suggest that near daily cannabis use may increase symptoms of anxiety, mania and hypomania (in BD patients), and severity of PTSD symptoms (National Academy of Sciences, Engineering and Medicine, 2017).

Cannabis has also been associated with neurocognitive impairments involving transient deficits in short-term memory, judgment, and motor coordination (Volkow et al., 2014). Operating a motor vehicle after using cannabis has been reported as especially dangerous as cannabis has been associated with delayed reaction times, decreased hand-eye coordination, and altered time perception. Taken together, these factors may reduce the practicality of cannabis as a long-term treatment option. Further, long-term cannabis use has been associated with neuroanatomical alterations in brain regions with high CB_1 receptor density. This would include areas such as the hippocampus, amygdala and striatum, orbitofrontal cortex, parietal cortex, insular cortex, and cerebellum. Consequently, regular cannabis use during adolescence can be especially dangerous as the brain is still developing. Regular cannabis use prior to age 25 has been associated with altered brain development, and long-term or heavy use has been associated with poor educational outcome, cognitive impairment (lower IQs), diminished life satisfaction and achievement, and addiction (Volkow et al., 2014).

The addictiveness of cannabis also remains a controversial issue, as many view the substance as nonaddictive. However, the prevalence of cannabis use disorder is rising, with 2.7 million people (age 12 or older) meeting criteria for DSM-IV dependence in 2012 (Center for Behavioural Health Statistics and Quality, 2015). With policies shifting toward legalization for recreational use, many are projecting the prevalence of cannabis use to increase as it has in the 28 U.S. states where it is presently authorized for medical purposes (Cerdá, Wall, Keyes, Galea, & Hasin, 2012; Hasin et al., 2015; Wall et al., 2011). The widespread exposure of cannabis may also soon add to the increased burden of disease that has typically been associated with other legal substances such as alcohol and tobacco (Degenhardt & Hall, 2012). Existing reports indicate that the odds of cannabis abuse/dependence were 1.81 times higher (95%CI: 1.22–2067; $P = .0040$) among residents of states with legalized medical marijuana, compared to those without (Cerdá et al., 2012). Further, using data from the National Survey of Drug Use and Health, more medical marijuana users (33%) reported daily or almost daily cannabis intake compared to recreational users (11%), and up to 11% of medical marijuana users met criteria for DSM-IV cannabis abuse/dependence (Lin, Ilgen, Jannausch, & Bohnert, 2016). In contrast, in a sample of 868 adult primary care patients, those who reported medical marijuana use had similar scores on the Addiction Severity Index Lite to those who used marijuana recreationally (Roy-Byrne et al., 2015). Medical marijuana users also reported lower scores on the Drug Abuse Screening Test and had a greater frequency of medical problems compared to recreational users although the rates of psychiatric disorders were similar between groups (Roy-Byrne et al., 2015).

5 | DISCUSSION

The evidence supporting use of cannabis as a psychopharmacological treatment for anxiety, mood and related disorders appears to be comprised of a few, primarily single-dose studies. Unfortunately, these studies have small sample sizes, as well as deficits in the overall study designs which limit the clinical application of findings. For example, although the studies allude to an anxiolytic effect of the cannabinoid compound following a single dose, in order for the agent to be considered a potentially efficacious treatment, it would require an actual treatment trial with repeated regular administration in an ill population. A longer follow-up phase would also need to be incorporated, as existing studies fail to demonstrate the maintenance of any reported acute treatment gains. Most importantly, although cannabinoid agents have been examined, the current literature has not effectively evaluated plant-based cannabis: the primary compound used in the community. Nevertheless, the cannabis and cannabinoid literature has been ranked according to four levels of evidence, as defined in the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Lam et al., 2016) (Table 1). Using these criteria, the evidence supporting cannabinoids do not rank higher than Level 3 for SAD, GAD, PTSD, trichotillomania, and TS, given the small sample sizes and that many are single dose, rather than treatment studies. For OCD, BD, and MDD, the evidence would be considered Level 4. With benefits to mental health supported by limited evidence, coupled with the risks associated with regular use, it may be difficult to objectively place cannabis in the armamentarium of psychopharmacological treatments until further research is conducted and treatment guidelines developed. Although the results of existing studies support a role for the endocannabinoid system in the pathophysiology of anxiety disorders, without evaluating the effects of the plant as a whole, no recommendations can be made on the clinical utility of cannabis as a treatment for these conditions. Furthermore, there are several important issues which remain unclear, such as delineating the specific effects of numerous cannabis strains as each strain varies in cannabinoid content and potency, and consequently may be associated with a variety of psychological and physiological effects. In addition, cannabis is seldom used independently and is most typically paired with alcohol consumption (Downey et al., 2013). Therefore, the interactions between cannabis and other medications and recreational substances should also be examined as patients may be at an increased risk for further negative consequences of use. Other important issues including frequency, dosage, time of intake, mode of delivery, and patient characteristics are also unknown (D'Souza & Ranganathan, 2015). For instance, would cannabis be best utilized as a standalone treatment or as an adjunct to standard treatments? What patient populations (based on age and clinical presentation) should it be used in? Are physicians to prescribe cannabis for treatment simply to patients who present interest or only to those who are refractory to traditional treatments? In either situation one must consider whether the therapeutic benefits of cannabis are comparable to other traditional psychopharmacological treatments (i.e., SSRIs) especially with the effects of long-term repeated cannabis exposure not being as well characterized as its acute effects (D'Souza & Ranganathan, 2015).

Interestingly, many of these questions also exist for conditions which have regulatory authorization for medical use in some jurisdictions, as is the case for both PTSD and TS. Although TS and PTSD possess the largest bodies of evidence evaluating the effects of synthetic cannabinoids, such as nabilone and dronabinol, the efficacy of

TABLE 1 Levels of evidence for cannabis and cannabinoids as treatment

Condition	Compound	Levels of evidence	Highest level
Social anxiety disorder	Cannabis CBD THC Synthetic cannabinoids	 3 	3
Generalized anxiety disorder	Cannabis CBD THC Synthetic cannabinoids	 3 (nabilone)	3
Major depressive disorder	Cannabis CBD THC Synthetic cannabinoids	4 -3 4	4
Bipolar disorder	Cannabis CBD THC Synthetic cannabinoids	4 -4 	4
Posttraumatic stress disorder	Cannabis CBD THC Synthetic cannabinoids	3 3 3 (nabilone)	3
Obsessive-compulsive disorder	Cannabis CBD THC Synthetic cannabinoids	 4 (Adj. dronabinol)	4
Trichotillomania	Cannabis CBD THC Synthetic cannabinoids	 3	3
Tourette's disorder	Cannabis CBD THC Synthetic cannabinoids	4 3 	3

1, Meta-analysis with narrow confidence intervals and/or two or more RCTs with adequate sample size, preferably placebo controlled.
2, Meta-analysis with wide confidence intervals and/or one or more RCTs with adequate sample size.
3, Small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series, *or* high-quality retrospective studies.
-3, Negative, small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series, *or* high-quality retrospective studies.
4, Expert opinion/consensus.
-4, Negative, case report.

smoked or vaporized cannabis remains unknown. Although synthetic homologues of THC act on the same receptor system, the constituents alone are likely not responsible for the observed effects of the smoked plant. Instead, it is more likely to be the cumulative effect of interactions between the hundreds of different compounds present in the plant. Moreover, the pharmacokinetics of such synthetic cannabinoids also differ from the natural product and are accountable for the varying physiological effects of each respective compound (Cooper et al., 2013). Finally, the reported benefits in PTSD also seem to be limited primarily to improvements in sleep disturbances. Although the literature regarding the effects of cannabinoids on sleep is extensive (reviewed in Gates, Albertella, & Copeland, 2014) it may be of interest to examine such issues in anxious and depressed populations given the high prevalence of sleep disturbances in these groups.

6 | FUTURE DIRECTIONS

With cannabis legalization for medical and recreational use becoming more widespread, it is crucial that research work toward establishing evidence. As is the case for many alternative treatments there is a pervasive belief surrounding the anxiolytic and euphoriant effects of cannabis, however, the actual science appears to have been outpaced by the development of applicable legislation and public opinion. Further, the documented mental health effects associated with cannabis use also create cause for concern as existing symptomatology typically worsens with use and incidence of certain psychiatric conditions increases (NASEM, 2017). Moreover, there is little observational evidence demonstrating improvement in mental health conditions with cannabis use (NASEM, 2017). Clinicians are consequently ill equipped to offer evidence-based advice regarding cannabis' utility as a mental health treatment.

The potential role of cannabis as both an adjunct to traditional treatments and as a standalone treatment requires RCT evaluation in specific conditions, using well-characterized strains. Beyond the required clinical studies, those examining the associated neural circuitry, predictors of response for specific anxiety, and mood disorders will help better illuminate the role of cannabis in treating these conditions. Similarly, efforts to attempt clinical characterization of patients

with unfavorable responses to cannabis would also be of great impact. Nevertheless, there is some evidence to support the use of CBD (in SAD) and THC (in PTSD), however at this stage, there appears to be little evidence to support the use of the cannabis plant as a treatment for anxiety, mood and related conditions.

REFERENCES

Ablon, S. L., & Goodwin, F. K. (1974). High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. *American Journal of Psychiatry*, *131*(4), 448–453.

Ashton, H., Golding, J., Marsh, V. R., Millman, J. E., & Thompson, J. W. (1981). The seed and the soil: Effect of dosage, personality and starting state on the response to delta 9 tetrahydrocannabinol in man. *British Journal of Clinical Pharmacology*, *12*(5), 705–720.

Aso, E., Ozaita, A., Serra, M. À., & Maldonado, R. (2011). Genes differentially expressed in CB 1 knockout mice: Involvement in the depressive-like phenotype. *European Neuropsychopharmacology*, *21*(1), 11–22.

Bandelow, B., Zohar, J., Hollander, E., Kasper, S., Moeller, H., & WFSBP Task Force Treatment Guidelines. (2008). World federation of societies of biological psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—First revision. *World Journal of Biological Psychiatry*, *9*, 248–312

Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., de Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F., … Martín-Santos, R. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology*, *36*(6), 1219–1226.

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., … Mehta, M. A. (2010). Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*, *35*(3), 764–774.

Blass, K. (2008). *Treating depression with cannabinoids (Cannabinoids 3)*. Washington, DC: US Government Printing Office.

Blessing, E. M., Steenkamp, M. M., Manzanares, J., & Marmar, C. R. (2015). Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics*, *12*, 825–836.

Bonn-Miller, M. O., Babson, K. A., & Vandrey, R. (2014). Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. *Drug and alcohol Dependence*, *136*, 162–165.

Bonn-Miller, M. O., Zvolensky, M. J., & Bernstein, A. (2007). Marijuana use motives: Concurrent relations to frequency of past 30-day use and anxiety sensitivity among young adult marijuana smokers. *Addictive Behaviors*, *32*(1), 49–62.

Bossong, M. G., van Hell, H. H., Jager, G., Kahn, R. S., Ramsey, N. F., & Jansma, J. M. (2013). The endocannabinoid system and emotional processing: A pharmacological fMRI study with∆ 9-tetrahydrocannabinol. *European Neuropsychopharmacology*, *23*(12), 1687–1697.

Cameron, C., Watson, D., & Robinson, J. (2014). 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*, *34*(5), 559–564.

Campolongo, P., Roozendaal, B., Trezza, V., Hauer, D., Schelling, G., McGaugh, J. L., & Cuomo, V. (2009). Endocannabinoids in the rat basolateral amygdala enhance memory consolidation and enable glucocorticoid modulation of memory. *Proceedings of the National Academy of Sciences*, *106*(12), 4888–4893.

Casarotto, P. C., Gomes, F. V., Resstel, L. B., & Guimarães, F. S. (2010). Cannabidiol inhibitory effect on marble-burying behaviour: Involvement of CB1 receptors. *Behavioural Pharmacology*, *21*(4), 353–358. Retrieved from https://doi.org/10.1097/fbp.0b013e32833b33c5

Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 national survey on drug use and health (HHS publication no. SMA 15–4927, NSDUH series H-50). Retrieved from http://www.samhsa.gov/data/

Cerdá, M., Wall, M., Keyes, K. M., Galea, S., & Hasin, D. (2012). Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and Alcohol Dependence*, *120*(1–3), 22–27. Retrieved from https://doi.org/10.1016/j.drugalcdep.2011.06.011

Cheung, J. T., Mann, R. E., Ialomiteanu, A., Stoduto, G., Chan, V., Ala-Leppilampi, K., & Rehm, J. (2010). Anxiety and mood disorders and cannabis use. *American Journal of Drug and Alcohol Abuse*, *36*(2), 118–122.

Chhatwal, J. P., Davis, M., Maguschak, K. A., & Ressler, K. J. (2005). Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. *Neuropsychopharmacology*, *30*(3), 516–524.

Cooper, Z. D., Comer, S. D., & Haney, M. (2013). Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers. *Neuropsychopharmacology*, *38*(10), 1984–1992.

Cougle, J. R., Bonn-Miller, M. O., Vujanovic, A. A., Zvolensky, M. J., & Hawkins, K. A. (2011). Posttraumatic stress disorder and cannabis use in a nationally representative sample. *Psychology of Addictive Behaviors*, *25*(3), 554–558.

Crippa, J. A., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L., Martin-Santos, R., … Santos Filho, A. (2011). Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. *Journal of Psychopharmacology*, *25*(1), 121–130.

Crippa, J. A., Zuardi, A. W., Garrido, G. E., Wichert-Ana, L., Guarnieri, R., Ferrari, L., … Busatto, G. F. (2004). Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*, *29*(2), 417–426

Crippa, J. A., Zuardi, A. W., Martín-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., & Fusar-Poli, P. (2009). Cannabis and anxiety: A critical review of the evidence. *Human Psychopharmacology: Clinical and Experimental*, *24*(7), 515–523.

Das, R. K., Kamboj, S. K., Ramadas, M., Yogan, K., Gupta, V., Redman, E., … Morgan, C. J. (2013). Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology*, *226*(4), 781–792.

Degenhardt, L., & Hall, W. (2012). Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet*, *379*(9810), 55–70. Retrieved from https://doi.org/10.1016/s0140-6736(11)61138-0

Downey, L. A., King, R., Papafotiou, K., Swann, P., Ogden, E., Boorman, M., & Stough, C. (2013). The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. *Accident Analysis and Prevention*, *50*, 879–886. Retrieved from https://doi.org/10.1016/j.aap.2012.07.016

D'Souza, D. C. (2016, May). Medical Cannabis: For which conditions and under what circumstances? Presented at the American Psychiatric Association Meeting, Atlanta, GA.

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., … Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology*, *29*(8), 1558–1572.

D'souza, D. C., & Ranganathan, M. (2015). Medical marijuana: Is the cart before the horse? *JAMA*, *313*(24), 2431–2432

Fabre, L. F., & McLendon, D. (1981). The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *Journal of Clinical Pharmacology*, *21*(S1), 377S–382S.

Feingold, D., Weiser, M., Rehm, J., & Lev-Ran, S. (2015). The association between cannabis use and mood disorders: A longitudinal study. *Journal of Affective Disorders*, *172*, 211–218.

Fraser, G. (2009). The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in post-traumatic stress disorder (PTSD). *CNS Neuroscience and Therapeutics*, *15*, 84–88.

Fusar-Poli, P. (2009). S39-01 Distinct effects of D9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *European Psychiatry*, *24*, S206.

Fusar-Poli, P., Allen, P., Bhattacharyya, S., Crippa, J. A., Mechelli, A., Borgwardt, S., … Zuardi, A. W. (2010). Modulation of effective connectivity during emotional processing by Δ9-tetrahydrocannabinol and cannabidiol. *International Journal of Neuropsychopharmacology*, *13*(4), 421–432.

Gates, P. J., Albertella, L., & Copeland, J. (2014). The effects of cannabinoid administration on sleep: A systematic review of human studies. *Sleep Medicine Reviews*, *18*(6), 477–487.

Gibbs, M., Winsper, C., Marwaha, S., Gilbert, E., Broome, M., & Singh, S. P. (2015). Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders*, *171*, 39–47.

Glass, R. M., Uhlenhuth, E. H., Hartel, F. W., Schuster, C. R., & Fischman, M. W. (1981). Single-dose study of nabilone in anxious volunteers. *Journal of Clinical Pharmacology*, *21*(S1), 383S–396S.

Gomes, F. V., Casarotto, P. C., Resstel, L. B., & Guimarães, F. S. (2011). Facilitation of CB1 receptor-mediated neurotransmission decreases marble burying behavior in mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(2), 434–438. Retrieved from https://doi.org/10.1016/j.pnpbp.2010.11.027

Gorzalka, B. B., & Hill, M. N. (2011). Putative role of endocannabinoid signaling in the etiology of depression and actions of antidepressants. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(7), 1575–1585.

Grant, J. E., Odlaug, B. L., Chamberlain, S. R., & Kim, S. W. (2011). Dronabinol, a cannabinoid agonist, reduces hair pulling in trichotillomania: A pilot study. *Psychopharmacology*, *218*(3), 493–502. Retrieved from https://doi.org/10.1007/s00213-011-2347-8

Grant, S., Pedersen, E. R., & Neighbors, C. (2016). Associations of posttraumatic stress disorder symptoms with marijuana and synthetic cannabis use among young adult US Veterans: A pilot investigation. *Journal of Studies on Alcohol and Drugs*, *77*(3), 509–514.

Greer, G. R., Grob, C. S., & Halberstadt, A. L. (2014). PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *Journal of Psychoactive Drugs*, *46*(1), 73–77.

Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics*, *42*(4), 327–360.

Gruber, A. J., Pope, H. G., & Brown, M. E. (1996). Do patients use marijuana as an antidepressant. *Depression*, *4*(2), 77–80.

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Olson, D. P., Centorrino, F., & Lukas, S. E. (2012). Marijuana impacts mood in bipolar disorder: A pilot study. *Mental Health and Substance Use*, *5*(3), 228–239.

Hasin, D. S., Wall, M., Keyes, K. M., Cerdá, M., Schulenberg, J., O'malley, P. M., … Feng, T. (2015). Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: Results from annual, repeated cross-sectional surveys. *Lancet Psychiatry*, *2*(7), 601–608. Retrieved from https://doi.org/10.1016/s2215-0366(15)00217-5

Health Canada (2005). Fact Sheet – Sativex Retrieved from http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/sativex_fs_fd_091289-eng.php

Health Canada (2016). Consumer Information - Marijuana. Retrieved from https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/marihuana/info/cons-eng.pdf

Hemming, M., & Yellowlees, P. M. (1993). Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology*, *7*(4), 389–391. Retrieved from https://doi.org/10.1177/026988119300700041

Henquet, C., Krabbendam, L., de Graaf, R., ten Have, M., & van Os, J. (2006). Cannabis use and expression of mania in the general population. *Journal of Affective Disorders*, *95*, 103–110.

Hill, M. N., & McEwen, B. S. (2009). Endocannabinoids: The silent partner of glucocorticoids in the synapse. *Proceedings of the National Academy of Sciences*, *106*(12), 4579–4580.

Ilaria, R. L., Thornby, J. I., & Fann, W. E. (1981). Nabilone, a cannabinol derivative, in the treatment of anxiety neurosis. *Current Therapeutic Research, Clinical and Experimental*, *29*(6), 943–949.

Iskedjian, M., Bereza, B., Gordon, A., Piwko, C., & Einarson, T. R. (2007). Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Current Medical Research and Opinion*, *23*(1), 17–24.

Jetly, R., Heber, A., Fraser, G., & Boisvert, D. (2015). The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*, *51*, 585–588. Retrieved from https://doi.org/10.1016/j.psyneuen.2014.11.002

Johnson, M. J., Pierce, J. D., Mavandadi, S., Klaus, J., Defelice, D., Ingram, E., & Oslin, D. W. (2016). Mental health symptom severity in cannabis using and non-using Veterans with probable PTSD. *Journal of Affective Disorders*, *190*, 439–442.

Karniol, I. G., Shirakawa, I., Kasinski, N., Pfeferman, A., & Carlini, E. A. (1974). Cannabidiol interferes with the effects of Δ 9-tetrahydrocannabinol in man. *European Journal of Pharmacology*, *28*(1), 172–177.

Katzman, M. A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., & Van Ameringen, M. (2014). Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, *14*(1), 1–83.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). "Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication." *Archives of General Psychiatry 62*, 593–602

Kevorkian, S., Bonn-Miller, M. O., Belendiuk, K., Carney, D. M., Roberson-Nay, R., & Berenz, E. C. (2015). Associations among trauma, posttraumatic stress disorder, cannabis use, and cannabis use disorder in a nationally representative epidemiologic sample. *Psychology of addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*, *29*(3), 633–668.

Kotin, J., Post, R. M., & Goodwin, F. K. (1973). Δ9-Tetrahydrocannabinol in depressed patients. *Archives of General Psychiatry*, *28*(3), 345–348. Retrieved from https://doi.org/10.1001/archpsyc.1973.01750330041007

Ksir, C., & Hart, C. L. (2016). Cannabis and psychosis: A critical overview of the relationship. *Current Psychiatry Reports*, *18*(2), 1–11. Retrieved from https://doi.org/10.1007/s11920-015-0657-y

Lam, R. W., McIntosh, D., Wang, J., Enns, M. W., Kolivakis, T., Michalak, E. E., … Milev, R. V. (2016). Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 1. Disease burden and principles of care. *Canadian Journal of Psychiatry*, *61*(9), 510–523.

Lee, M. (2009). Anxiolytic effect of an oral cannabinoid in patients with anxiety. *European Journal of Pain*, *13*, S200–S201.

Lin, L. A., Ilgen, M. A., Jannausch, M., & Bohnert, K. M. (2016). Comparing adults who use cannabis medically with those who use recreationally: Results from a national sample. *Addictive Behaviors*, *61*, 99–103.

Lipschitz, D. S., Rasmusson, A. M., Anyan, W., Gueorguieva, R., Billingslea, E. M., Cromwell, P. F., & Southwick, S. M. (2003). Posttraumatic stress

disorder and substance use in inner-city adolescent girls. *Journal of Nervous and Mental Disease*, *191*(11), 714–721.

Machado Rocha, F. C., Stefano, S. C., De Cassia Haiek, R., Rosa Oliveira, L. M. Q., & Da Silveira, D. X. (2008). Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: Systematic review and meta-analysis. *European Journal of Cancer Care*, *17*(5), 431–443.

Martín-Sánchez, E., Furukawa, T. A., Taylor, J., & Martin, J. L. R. (2009). Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Medicine*, *10*(8), 1353–1368.

Martin-Santos, R., Crippa, J. A., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., … Zuardi, A. W. (2012). Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. *Current Pharmaceutical Design*, *18*(32), 4966–4979.

Martyn, C. N., Illis, L. S., & Thom, J. (1995). Nabilone in the treatment of multiple sclerosis. *Lancet*, *345*(8949), 579.

Mashiah, M. (2012, Apr). *Medical cannabis as treatment for chronic combat PTSD: Promising results in an open label pilot study*. Presentation at patients out of time conference, Tuscon, AZ.

Mechoulam, R., & Parker, L. A. (2013). The endocannabinoid system and the brain. *Annual Review of Psychology*, *64*, 21–47.

Müller-Vahl, K. R., Kolbe, H., Schneider, U., & Emrich, H. M. (1998). Cannabinoids: Possible role in patho-physiology and therapy of Gilles de la Tourette syndrome. *Acta Psychiatrica Scandinavica*, *98*(6), 502–506. Retrieved from https://doi.org/10.1111/j.1600-0447.1998.tb10127.x

Müller-Vahl, K. R., Schneider, U., Koblenz, A., Jöbges, M., Kolbe, H., Daldrup, T., & Emrich, H. M. (2002). Treatment of Tourette's syndrome with Δ9-tetrahydrocannabinol (THC): A randomized crossover trial. *Pharmacopsychiatry*, *35*(2), 57–61. Retrieved from https://doi.org/10.1055/s-2002-25028

Muller-Vahl, K. R., Schneider, U., Kolbe, H., & Enrich, H. (1999). Treatment of tourette's syndrome with delta-9-tetrahydrocannbinol. *American Journal of Psychiatry*, *156*(3), 495.

Müller-Vahl, K. R., Schneider, U., Prevedel, H., Theloe, K., Kolbe, H., Daldrup, T., & Emrich, H. M. (2003). Δ9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *Journal of Clinical Psychiatry*, *64*(4), 459–465.

National Academies of Sciences, Engineering, and Medicine. (2017). Mental Health. In E. Bass, J. P. Caulkins, M. D'Alton, R. Gonzalez, F. F. Furstenberg, E. Evins, … J. H. Krystal (Eds.), *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research* (pp. 289–327). Washington: DC: National Academies Press.

Neumeister, A., Normandin, M. D., Pietrzak, R. H., Piomelli, D., Zheng, M. Q., Gujarro-Anton, A., … Ropchan, J. (2013). Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: A positron emission tomography study. *Molecular Psychiatry*, *18*(9), 1034–1040.

Olfson, M., Marcus, S. C., Tedeschi, M., & Wan, G. J. (2006). Continuity of antidepressant treatment for adults with depression in the United States. *American Journal of Psychiatry*, *163*(1), 101–108.

Pacher, P., Bátkai, S., & Kunos, G. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological Reviews*, *58*(3), 389–462.

Passie, T., Emrich, H. M., Karst, M., Brandt, S. D., & Halpern, J. H. (2012). Mitigation of post-traumatic stress symptoms by Cannabis resin: A review of the clinical and neurobiological evidence. *Drug Testing and Analysis*, *4*(7–8), 649–659.

Phan, K. L., Angstadt, M., Golden, J., Onyewuenyi, I., Popovska, A., & de Wit, H. (2008). Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *Journal of Neuroscience*, *28*(10), 2313–2319.

Phillips, T. J., Cherry, C. L., Cox, S., Marshall, S. J., & Rice, A. S. (2010). Pharmacological treatment of painful HIV-associated sensory neuropathy: A systematic review and meta-analysis of randomised controlled trials. *PLoS One*, *5*(12), e14433.

Pond, D. A. (1948). Psychological effects in depressive patients of the marihuana homologue synhexyl. *Journal of Neurology, Neurosurgery and Psychiatry*, *11*(4), 271–279.

Public Health Agency of Canada (2012). A report on mental illnesses in Canada. Retrieved from http://www.phac-aspc.gc.ca/publicat/miic-mmac/sum-eng.php

Rabinak, C. A., Angstadt, M., Lyons, M., Mori, S., Milad, M. R., Liberzon, I., & Phan, K. L. (2014). Cannabinoid modulation of prefrontal–limbic activation during fear extinction learning and recall in humans. *Neurobiology of Learning and Memory*, *113*, 125–134.

Rabinak, C. A., Angstadt, M., Sripada, C. S., Abelson, J. L., Liberzon, I., Milad, M. R., & Phan, K. L. (2013). Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology*, *64*, 396–402.

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future. *Biological Psychiatry*, *60*(4), 376–382.

Regelson, W., Butler, J. R., Schulz, J., Kirk, T., Peek, L., Green, M. L., & Zalis, M. O. (1976). Delta 9-THC as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In M. C. Braude & S. Szara (Eds.), *The Pharmacology of Marihuana* (pp, 763–776). New York: Raven Press.

Reinarman, C., Nunberg, H., Lanthier, F., & Heddleston, T. (2011). Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs*, *43*(2), 128–135.

Reznik, I. (2011). Medical cannabis use in post-traumatic stress disorder: A naturalistic observational study. *Abstract presented at the cannabinoid conference. Bonn, Germany*. 8–10.

Rock, E. M., Bolognini, D., Limebeer, C. L., Cascio, M. G., Anavi-Goffer, S., Fletcher, P. J., … Parker, L. A. (2012). Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT1A somatodendritic autoreceptors in the dorsal raphe nucleus. *British Journal of Pharmacology*, *165*(8), 2620–2634.

Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation*, *34*(8), 587–591.

Roy-Byrne, P., Maynard, C., Bumgardner, K., Krupski, A., Dunn, C., West, I. I., … Ries, R. (2015). Are medical marijuana users different from recreational users? The view from primary care. *American Journal on Addictions*, *24*(7), 599–606.

Sandyk, R., & Awerbuch, G. (1988). Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology*, *8*(6), 444–445. Retrieved from https://doi.org/10.1097/00004714-198812000-00021

Schindler, F., Anghelescu, I., Regen, F., & Jockers-Scherubl, M. (2008). Improvement in refractory obsessive compulsive disorder with dronabinol. *American Journal of Psychiatry*, *165*(4), 536–537. Retrieved from https://doi.org/10.1176/appi.ajp.2007.07061016

Sethi, B. B., Trivedi, J. K., Kumar, P., Gulati, A., Agarwal, A. K., & Sethi, N. (1986). Antianxiety effect of cannabis: Involvement of central benzodiazepine receptors. *Biological Psychiatry*, *21*(1), 3–10.

Stockings, G. T. (1947). A new euphoriant for depressive mental states. *British Medical Journal*, *1*(4512), 918–922.

Swift, W., Wong, A., Li, K. M., Arnold, J. C., & McGregor, I. S. (2013). Analysis of cannabis seizures in NSW, Australia: Cannabis potency and cannabinoid profile. *PloS one*, *8*(7), e70052.

Thomas, A., Baillie, G. L., Phillips, A. M., Razdan, R. K., Ross, R. A., & Pertwee, R. G. (2007). Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *British Journal of Pharmacology*, *150*(5), 613–623.

Valverde, O., & Torrens, M. (2012). CB1 receptor-deficient mice as a model for depression. *Neuroscience*, *204*, 193–206.

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, *370*(23), 2219–2227. Retrieved from https://doi.org/10.1056/nejmra1402309

Wade, D. T., Robson, P., House, H., Makela, P., & Aram, J. (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clinical Rehabilitation*, *17*(1), 21–29.

Wall, M. M., Poh, E., Cerdá, M., Keyes, K. M., Galea, S., & Hasin, D. S. (2011). Adolescent marijuana use from 2002 to 2008: Higher in states with medical marijuana laws, cause still unclear. *Annals of Epidemiology*, *21*(9), 714–716. Retrieved from https://doi.org/10.1016/j.annepidem.2011.06.001

Walsh, Z., Callaway, R., Belle-Isle, L., Capler, R., Kay, R., Lucas, P., & Holtzman, S. (2013). Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. *International Journal of Drug Policy*, *24*(6), 511–516.

Walsh, Z., Gonzalez, R., Crosby, K., Thiessen, M. S., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. *Clinical Psychology Review*, *51*, 15–29.

Wilkinson, S. T., Stefanovics, E., & Rosenheck, R. A. (2015). Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *Journal of Clinical Psychiatry*, *76*(9), 1174–1180. Retrieved from https://doi.org/10.4088/jcp.14m09475

World Health Organization (2016). *Management of Substance abuse: Cannabis*. Retrieved from http://www.who.int/substance_abuse/facts/cannabis/en/

Wu, K., Hanna, G. L., Rosenberg, D. R., & Arnold, P. D. (2012). The role of glutamate signaling in the pathogenesis and treatment of obsessive–compulsive disorder. *Pharmacology Biochemistry and Behavior*, *100*(4), 726–735. Retrieved from https://doi.org/10.1016/j.pbb.2011.10.007

Zuardi, A. W. (2008). Cannabidiol: From an inactive cannabinoid to a drug with wide spectrum of action. *Revista brasileira de psiquiatria*, *30*(3), 271–280.

Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimaraes, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology*, *7*(1 Suppl), 82–88.

Zuardi, A. W., Crippa, J. A. S., Dursun, S. M., Morais, S. L., Vilela, J. A. A., Sanches, R. F., & Hallak, J. E. C. (2010). Cannabidiol was ineffective for manic episode of bipolar affective disorder. *Journal of Psychopharmacology*, *24*(1), 135–137.

Zuardi, A. W., Shirakawa, I., Finkelfarb, E., & Karniol, I. G. (1982). Action of cannabidiol on the anxiety and other effects produced by Δ9-THC in normal subjects. *Psychopharmacology*, *76*(3), 245–250.

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