The Effectiveness of Cannabinoids in the Treatment of Posttraumatic Stress Disorder (PTSD): a Systematic Review

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Short title: Cannabinoids for the treatment of PTSD

Abstract

Objectives: Post-traumatic stress disorder (PTSD) is a potentially debilitating mental health problem. There has been a recent surge of interest regarding the use of cannabinoids in the treatment of PTSD. We therefore sought to systematically review and assess the quality of the clinical evidence of the effectiveness of cannabinoids for the treatment of PTSD.

Method: We included all studies published until December 2018 where a patient has been diagnosed with PTSD and had been prescribed or were using a cannabinoid for the purpose of reducing PTSD symptoms. Our primary outcome measure was the reduction in PTSD symptoms using a validated instrument. In the absence of randomized controlled trials, we included the next best available levels of evidence including observational and retrospective studies and case reports. We assessed risk of bias and quality using validated tools appropriate for the study design.

Results: We included 10 studies in this review, of which only one study was a pilot randomized, double-blind, placebo-controlled crossover, clinical trial. Every identified study had medium to high risk of bias and was of low quality. We found that cannabinoids may decrease PTSD symptomology, in particular sleep disturbances and nightmares.

Conclusions: Most studies to date are small and of low quality, with significant limitations to the study designs precluding any clinical recommendations about its use in routine clinical practice. Evidence that cannabinoids may help reduce global PTSD symptoms, sleep disturbances, and nightmares indicates that future well controlled, randomized, double-blind clinical trials are highly warranted.

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Keywords: Cannabis, THC, CBD, nabilone, Posttraumatic stress disorder, treatments.

Introduction

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a potentially debilitating condition. PTSD affects approximately 1% of the population (Karam et al., 2014) and is over-represented in military veterans (Richardson, Frueh, & Acierno, 2010). The fundamental features of PTSD include: (1) re-experiencing of the trauma through intrusive memories, flashbacks and/or nightmares; (2) active avoidance of external and internal reminders of the trauma and; (3) hyper-arousal (Brewin et al., 2017). At its core, PTSD can be conceptualized as a disorder of memory processing (Brewin, 2001, 2003). Treatment is generally focused on re-processing and re-appraisal of trauma memories and their sequelae through trauma-focused psychotherapies. Pharmacotherapy can also be offered. Currently approved and recommended drugs (NICE, 2018) include serotonin reuptake inhibitors and monoamine receptor antagonists to provide symptomatic relief. However, as many patients struggle to access expert trauma-focused therapies and have sub-optimal responses to these pharmacological treatments, there is an urgent need to develop new intervention strategies (Krystal, Rosenheck, & Cramer, 2011).

Within the context of a shifting legal and political backdrop across the world, there has been a surge in the use of cannabinoids for treating psychiatric disorders, including PTSD (Cougle et al., 2011). In the absence of clinical evidence, individuals with PTSD may be using cannabinoids as a means of coping or self-medication (Loflin, Earleywine, & Bonn-Miller, 2017; Metrik, Bassett, Aston, Jackson, & Borsari, 2018). The use of cannabinoids in mental health research has been considered controversial and the evidence base for its therapeutic effects is underdeveloped, largely mixed, and lacking randomized clinical trials (RCTs; Cousijn, Núñez, & Filbey, 2018). However, in the USA, the use of cannabinoids is approved for people suffering from PTSD in most states that permit "medical cannabis" (National Conferences of State Legislature, 2019). Thus, a fine-grained evaluation of the treatment potential of cannabinoids warranted. We will first briefly describe the pharmacology of cannabinoids and the rationale for considering cannabinoids in the treatment of PTSD. We will then systematically review the clinical evidence of the efficacy of cannabinoids in the treatment of PTSD

Cannabis and Cannabinoids

Cannabinoids act on the endogenous cannabinoid system (endocannabinoid system; eCB system); a neuromodulatory system which has many regulatory and homeostatic roles (Rodriguez de Fonseca et al., 2004; Volkow, Hampson, & Baler, 2017). The primary role of the eCB system is to modulate other neurotransmitter systems (Bloomfield, Ashok, Volkow, & Howes, 2016; Bloomfield et al., 2018). The eCB system comprises endogenous ligands (anandamide and 2-arachidonoylglycerol [2-AG]), cannabinoid receptors (type 1 [CB_1R] and type 2 [CB_2R]), and enzymes that catabolize the internal ligands (fatty acid amide hydrolase and [FAAH] and monoacylglycerol lipase [MAGL]). Activation of CB_1R, the most abundant class of G-protein coupled receptors in the central nervous system (Pertwee, 2008), suppresses neurotransmitter release. CB_1Rs are predominantly expressed on GABA and glutamate nerve terminals (Castillo, Younts, Chávez, & Hashimotodani, 2012) and are also found on serotonin, noradrenaline and dopamine-related nerve terminals (Castillo et al., 2012). The eCBs (anandamide & 2-AG) are released 'on demand' from the post-synaptic terminal and feedback in a retrograde manner onto the presynaptic terminal.

Current estimates suggest there are 104 phytocannabinoids present in the cannabis plant, the two most investigated of which are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Pertwee, 2008). THC is the primary psychoactive cannabinoid found in cannabis. CBD is non-intoxicating, has anxiolytic and antipsychotic properties, and a superior tolerability and side-effect profile in comparison to the cannabinoid type 1 receptor (CB_1R) agonists which include THC, nabilone and dronabinol (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Iffland & Grotenhermen, 2017). Strains of cannabis may be differently therapeutic due to variance in cannabinoid content with high-THC strains produce different effects in comparison to balanced THC:CBD strains. Indeed, CBD may reduce some of the psychogenic experiences produced by THC (Bhattacharyya et al., 2010; Russo & Guy, 2006).

Dronabinol and nabilone are synthetically produced medicinal products which mimic the effects of THC. Recently, the FDA approved Epidiolex (GW Pharmaceuticals), an oral CBD solution derived from the whole cannabis plant, for the treatment of seizures in two rare and severe forms of childhood epilepsy. These medications are different to what is available in US dispensaries or health food shops, in that they are highly regulated and differ in dosage (Bonn-Miller et al., 2017; Freeman, Hindocha, Green, & Bloomfield, 2019; Vandrey et al., 2015).

THC, dronabinol and nabilone act as CB_1R partial agonists (Felder, Veluz, Williams, Briley, & Matsuda, 1992). CBD, on the other hand, has a more complicated and elusive pharmacology. CBD acts of a wide range of targets and largely independently of the CB_1R (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015). Regarding the eCB system, CBD likely acts through negative allosteric modulation of the CB_1R and FAAH inhibition (Laprairie et al., 2015; Straiker, Dvorakova, Zimmowitch, & Mackie, 2018). CBD modulates 5-HT_{1A} (Russo, Burnett, Hall, & Parker, 2005), GPR55 (Ryberg et al., 2007), the μ-and δ-opioid receptors (Kathmann, Flau, Redmer, Trankle, & Schlicker, 2006), the transient receptor potential cation channel V1 (TRPV1) (Bisogno et al., 2001), peroxisome proliferator-activated receptor gamma (PPAR-□□ (Campos, Moreira, Gomes, Del Bel, & Guimaraes, 2012), and dopamine D_2 receptors (Seeman, 2016).

Amongst the most studied functions of the eCB system are its effect on stress regulation and anxiety (Morena, Patel, Bains, & Hill, 2016; Ruehle, Rey, Remmers, & Lutz, 2012; Trezza & Campolongo, 2013; Viveros, Marco, & File, 2005) and pain regulation (Calignano, La Rana, Giuffrida, & Piomelli, 1998; Volkow et al., 2017; Woodhams, Sagar, Burston, & Chapman, 2015) both of which are important in relation to treating individuals with PTSD.

Cannabinoids for the treatment of PTSD

PTSD has been prioritized by the National Academies of Sciences, Engineering and Medicine Report on Cannabinoids as an important area of investigation, which suggests a sense of urgency in the investigation of cannabinoids for the treatment of PTSD (Cousijn et al., 2018; National Academies of Sciences & Medicine, 2017). Boden, Babson, Vujanovic, Short, and Bonn-Miller (2013) found that participants with a diagnosis of PTSD, in comparison to those without, report greater use of cannabis to cope but also greater severity of withdrawal from cannabis. Observational evidence suggests that people are self-treating with cannabis; there is a vast array of anecdotal accounts and case reports that suggest using “medical cannabis” can dramatically reduce PTSD-related symptomology such as sleep disturbances (Bonn-Miller, Babson, & Vandrey, 2014). Self-report data from those attending US cannabis dispensaries suggest that cannabinoids may help with PTSD associated traumatic intrusions, hyper-arousal, stress, anxiety, depression, and insomnia (Bonn-Miller, Boden, Bucossi, & Babson, 2014). Whilst this evidence may be subject to bias, such reports should not be ignored in light of the high levels of suffering associated with PTSD and the absence of novel treatments in the pipeline.

There are several lines of evidence including imaging, peripheral biomarker studies, and genetics, that indicate the eCB system is involved in the pathophysiology of PTSD given its key role for the eCB system in stress and fear regulation (Hill, Miller, Carrier, Gorzalka, & Hillard, 2009; Hill & Patel, 2013; Hillard, Weinlander, & Stuhr, 2012; Neumeister et al., 2013; Volkow et al., 2017).

PTSD is characterized by amygdala hyper-reactivity, which contributes to the state of constant vigilance seen in patients with PTSD (Etkin & Wager, 2007; LeDoux, 2007; Yehuda & LeDoux, 2007). Excessive amygdala hyper-reactivity is likely to contribute to many PTSD symptoms (for a review see: Diamond & Zoladz, 2016; Zoladz & Diamond, 2016), including preventing re-integration of trauma memories (Ehlers & Clark, 2000) . CB_1Rs, upon which THC acts, are highly expressed within the amygdala (Herkenham et al., 1990). Amygdalar CB_1R availability specifically was related to attentional bias to threat; a key symptom in PTSD (Pietrzak et al., 2014).

Borne out of a large pre-clinical literature base which suggested that cannabinoids were modulating emotional memory, fear, and anxiety (Ruehle et al., 2012); Phan et al. (2008) and others (Bossong et al., 2013) found that a single acute dose of THC significantly reduced amygdala reactivity to social signals of threat. THC has also been shown to enhance amygdala-prefrontal connectivity, modulate subjective anxiety (dependent on dose), impair facial emotional processing, and increase fear extinction (Ballard, Bedi, & de Wit, 2012; D'Souza et al., 2004; Gorka, Fitzgerald, de Wit, & Phan, 2014; Hindocha et al., 2015; Rabinak et al., 2013). However, other research suggests that THC can increase amygdala reactivity to unpleasant images compared to neutral images, suggesting THC has a complex effect on amygdala reactivity and anxiety, where high doses can exacerbate anxiety (Gorka et al., 2015).

CBD, on the other hand, has been shown to modulate emotional and social processes (Bergamaschi et al., 2011; Hindocha et al., 2015) and enhance consolidation of extinction learning in humans. Therefore, CBD may have value as an adjunct to extinction-based therapies (Das et al., 2013). Moreover, long term use of cannabis can have detrimental outcomes on these processes which increase the risk of mental illnesses, including addiction and psychosis, and can impair executive functioning (for a review see Bloomfield et al. (2018).

In addition to the amygdala, the hippocampus is involved in the pathophysiology of PTSD (Elzinga and Bremner, 2002) as it plays a primary role in learning and memory, especially declarative or explicit memories. Aberrant fear learning, which is considered to be biased toward generalization of fear and is hippocampal dependent, contributes to PTSD. The hippocampus also plays an important role in the integration space and time in memory, which is disturbed in patients with PTSD and may underlie distortions and the fragmented nature of trauma memories (Bremner, Krystal, Charney, & Southwick, 1996; Bremner, Southwick, Darnell, & Charney, 1996). CB_1Rs are densely expressed in the hippocampus (Chan, Hinds, Impey, & Storm, 1998). A positron emission topography (PET) study found elevated CB_1R availability in patients with PTSD (Neumeister et al., 2013). Taken together, there is evidence that targeting the eCB system may be beneficial for treating PTSD.

In summary, PTSD is a potentially debilitating condition. It has been claimed that cannabinoids may have a role in the treatment of PTSD and there are plausible mechanisms through which cannabinoids may be capable of reducing PTSD symptoms. Within the context of previous systematic reviews in this area (Kansagara et al., 2017; Loflin, Babson, & Bonn-Miller, 2017; O'Neil et al., 2017; Steenkamp et al., 2017; Wilkinson et al., 2016), this review will harmonize evidence on synthetic cannabinoids (e.g., nabilone, dronabinol), pharmaceutically derived whole plant extracts (THC, CBD) and whole plant products (i.e., cannabis herbal and resin preparations, which are smoked). Importantly, this review evaluates the evidence using well-validated risk of bias and quality assessment tools that are appropriate for the papers being reviewed.

Methods

The following procedures were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, 1998; Moher, Liberati, Tetzlaff, Altman, & Group., 2009). This systematic review was prospectively registered on the National Institute for Health Research PROSPERO International Prospective Register of Systematic Reviews website (http://www.crd.york.ac.uk/prospero/; registration number:121646).

Information sources

Our search strategy involved terms that are related to cannabinoids as a treatment for PTSD which includes: nabilone, THC, CBD, and whole plant cannabis products (herbal and resin). We searched three electronic databases: “PsycINFO”, “PubMed”, “Embase”. We searched these databases using the OVID interface to find relevant studies. This search was conducted on December 10th, 2018r and completed on December 15th, 2018. We did not limit the date of publication in the search terms to ensure all relevant studies were retrieved. The reference lists of relevant eligible literature, including reviews and studies, were examined for additional relevant studies that were not available on the databases.

Search terms

Each search term within each concept was linked using the Boolean operator “OR” and each concept was combined together with the Boolean operator “AND”. The search string was as follows: (cannabis OR marijuana OR dronabinol OR nabilone OR cannabi* OR THC OR tetrahydrocannabi* OR Sativex OR cannabidiol OR epidiolex) AND (PTSD OR post-traumatic stress disorder OR trauma).

Eligibility criteria

Due to the dearth of clinical research related to cannabinoids in PTSD, inclusion criteria were broad to ensure that all relevant studies would be captured. Inclusion criteria were: 1) The patient has been diagnosed with PTSD using the Diagnostic and Statistical Manual (DSM) or the International Classification of Diseases (ICD) and/or via a validated Clinician-Administered PTSD psychometric symptom scale (such as the Clinical Administered PTSD scale [CAPS]) or patient-rated measures such as the PTSD Checklist (PCL); 2) Patients being prescribed or using a cannabinoid-based product (synthetic, whole plant extract or whole plant cannabis products (herbal and resin) for the purpose of reducing PTSD symptoms. Exclusion criteria were: 1) Studies not in English; 2) Animal studies. In the absence of RCTs, we included the next best available levels of evidence (e.g., observational and retrospective studies and case reports) in this review.

Outcome measures

We defined our primary outcome *a priori* as a reduction in PTSD symptoms as measured by any validated psychometric symptom scale measure of severity of symptoms. Common primary outcomes include the Clinician-Administered PTSD Scale (Blake et al., 1995) and PTSD Checklist (PCL) (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996), which has both a civilian (PCL-C) and military version (PCL-M), as well as one developed for DSM-5 (PCL-5). Any other measures relevant to mental wellbeing and functioning (including individual PTSD symptoms) were considered as secondary outcomes.

Study selection

We performed a preliminary search using the agreed search strategy and terms on the specified databases.Any duplicates were cross-checked and removed before the record titles and abstracts were screened by two reviewers individually (MR and CH), for inclusion. Where there was disagreement this was discussed with a third reviewer (MB) until consensus was reached. The full-text records and their respective reference lists were assessed independently with regard to suitability for inclusion in the review. Any discrepancies were resolved in discussion with the third reviewer.

Data collection process

For each study, we extracted the following data into Table 1.

1) Study (author and DOI); 2) Drug/Dose/Route of administration; 3) Type of study; 4) How the PTSD diagnosis was made for inclusion into the study and additional inclusion criteria; 5) Length of treatment; 6) Number of Participants; 7) Level of Evidence (Oxford Centre for Evidence-based Medicine – Levels of Evidence guideline; (Phillips et al., 2011)); 8) Primary outcome measure(s); 9) Primary outcome result; 10) Secondary outcome measures (related symptoms); 11) Secondary outcome results; 12) Adverse effects.

Risk of bias assessment (Table 2)

We assessed risk of bias using the Cochrane Risk of Bias (RoB) tool for RCTs, as recommended by the Cochrane Collaboration (Higgins et al., 2016). The eligible studies were assessed against seven key criteria which are: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants, 4) personnel and outcomes, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other sources of bias. With each of these criteria, the risk of bias in each study was rated as ‘low’, ‘high’, or ‘unclear’ risk of bias due to ambiguity or insufficient information. Risk of bias was assessed by two reviewers individually (MR and CH). Discrepancies were resolved in discussion with the third reviewer (MB).

Quality assessment (Tables 3 and 4)

We used the CONSORT Statement (Moher, 1998) as the framework for assessing and reporting the quality of the trials included in the review. The CONSORT Statement is comprised of a checklist of 25 items that focusses on how trials were designed, analyzed, and interpreted (see Table 3). Also, an 8-item checklist (Murad, Sultan, Haffar, & Bazerbachi, 2018) covering selection, ascertainment, causality, and reporting domains was used to assess the quality of case reports and case series included in this review (Table 4).

Effect size calculation

We calculated Cohen's *d* (Cohen, 1988) where sufficient data were presented in published data (see Table 1).

Results

Search selection

The details for the selection process are presented in the PRISMA flowchart in Figure 1. Through our search, we identified 10 studies that fit into the inclusion criteria. These studies investigated medicinal cannabinoids for patients suffering from PTSD and experiencing symptoms that were measured by a clinical psychometric.

[insert Figure 1]

Table 1 provides a summary of the 10 studies that met our inclusion criteria. One study was a pilot randomized, double-blind, placebo-controlled crossover, clinical trial. One study was a retrospective chart review. Two studies were retrospective case series. Three studies were open label, one of which was a clinical trial and two of which were pilot studies. One study was a naturalistic observational study, and two studies were observational clinical case studies. Three studies used nabilone, a synthetic THC analogue, one study used oral THC, two studies used CBD oil, and four studies used smoked herbal preparations of cannabis, including resin. Results will be discussed separately per cannabinoid compound.

[insert Table 1]

[insert Table 2]

[insert Table 3]

[insert Table 4]

Nabilone

Nabilone, a synthetic THC analogue, is a CB_1R agonist and has been used in three studies at varying doses. Nabilone was initially designed for chemotherapy induced nausea.

Jetly et al. (2015) reported on the effects of nabilone (oral; starting at 0.5mg/day increasing to 3mg/day) for 7 weeks, followed by a 2-week washout period and then another 7 weeks in Canadian military personnel suffering from PTSD. This study was the only placebo-controlled double-blind study; however, the CAPS total score was not reported as that study's primary outcome was the CAPS Recurring and Distressing Dreams subscale. Additionally, the trial was only in 10 individuals, but the crossover trial design allows for each subject to act as their own control, therefore reducing variability. This design also allows for analysis of the 2-week wash-out period to see if there is withdrawal or recurrence of symptoms – which there was not. A mean reduction in the CAPS score for Recurring and Distressing Dreams was found, and secondary measures of general wellbeing and global improvement followed. Although these results are encouraging, the crossover design did not allow for long-term follow up.

Cameron, Watson, and Robinson (2014) investigated the prescribing of nabilone in a retrospective chart review in 104 seriously mentally ill individuals in a correctional population. They found that for those given nabilone for the treatment of their PTSD symptoms, scores on the PTSD checklist-civilian version, decreased significantly, alongside greater increase in sleep and global function, reduction in nightmares, and increased global functioning. However, this is a patient-rated outcome, and a clinical assessment was not reported. Because this is a retrospective design, there was no systematic randomization to drug and there was no placebo or control group, which limits the conclusions that can be drawn. Additionally, since this sample was from "a severely mentally ill population within forensic services who were taking other psychotropic drugs", most of whom had a diagnosis of CUD, a major limitation of this study is its limited generalizability to others with PTSD and the difficulty to disentangle potential confounding effects from the effect of nabilone. It is important to note that this study noted potential severe side-effects of using nabilone in this population, in that two patients, both of whom had previous psychoses, experienced a recurrence of psychosis. All other side-effects were not serious, with the highest prevalence being sedation.

Fraser (2011) investigated nabilone in an open label clinical trial in 47 patients with PTSD treatment-resistant nightmares. Patients were administered a starting dose of 500 micrograms and were monitored weekly where the dose was adjusted up to 6mg nabilone nightly, based on efficacy and side-effects, with an effective dose of 200 micrograms to 4.0mg nightly. A total of 72% of patients reported complete cessation or reduction in nightmares accompanied by subjective improvements in sleep. Twenty-eight percent of patients withdrew from the study due to side effects. Upon discontinuation of nabilone, nightmares returned in 88% of the responder group within the first two nights. Beyond the open label design, a major limitation of this study is that they do not report the primary outcome with any statistical test.

THC

Roitman, Mechoulam, Cooper-Kazaz, and Shalev (2014) investigated the effects of 5mg sublingual THC twice a day, for three weeks, as an add-on treatment in an open label preliminary trial in 10 outpatients with chronic PTSD who were on stable medication (80% benzodiazepines). The primary aim was to investigate safety and tolerability of THC. THC was associated with statistically significant reductions in CAPS total scores as well as CAPS subscales for global functioning and nightmares, but not for avoidance or intrusions. There were no serious adverse effects reported and they also saw no change in physiological measures as a result of THC administration. Four of the patients (40%) reported mild adverse effects (e.g., dry mouth, headache, and dizziness) but did not discontinue treatment. There was no follow-up period and no control group, which precludes our ability to make conclusions about the effect of THC. No biological measure of THC absorption was assessed, so the amount of THC that was absorbed is unclear.

CBD

We found two studies that used CBD (Elms, Shannon, Hughes, & Lewis, 2018; Shannon & Opila-Lehman, 2016)

Elms et al. (2018) conducted a retrospective case series of 11 individuals with PTSD in an outpatient psychiatric clinic who were given CBD on a flexible dosing regimen. Patients completed the PTSD checklist for the DSM-5 (PCL-5) every 4 weeks for 8 weeks. Although the study does not report any statistical tests, it does report that the total reduction in symptoms was 28% across 8 weeks. In particular, CBD seemed to help patients with nightmares, a common symptom of their PTSD. The early end-point for descriptive statistics (i.e., % symptom reduction) makes it difficult to definitively determine whether continued use of CBD results in continued improvement of symptoms. Additionally, concurrent psychiatric medications were frequently added, removed or changed throughout the course of the study. The small sample size that was disproportionately female may represent selection bias at the clinic, which had a holistic approach to treatment including yoga and acupuncture. The CBD may have contained small traces of THC and other phytocannabinoids. There was no placebo or control group to compare the results too, so it is unclear how much of the effect is due to CBD and how much is due to other ongoing treatments. Furthermore, there was no biological marker of CBD absorption. Finally, given the recent public attention toward putative therapeutic effects of CBD and cannabis in general, it is unclear how much a placebo effect may have been driving the results. Indeed, there is evidence of changes in risk perception in the context of increasing legalization (Carliner, Brown, Sarvet, & Hasin, 2017).

Shannon et al (2016) reported a clinical case study of a 10-year-old girl with a diagnosis defined as “PTSD secondary to sexual abuse”. She was given CBD (25mg oral capsule) daily, for 6 months, plus ad-hoc sublingual CBD when needed. There was no primary outcome report of

PTSD symptomology. CBD was reported to reduce sleep disturbances and anxiety. Few conclusions can be drawn from this study.

Whole plant cannabis products (herbal or resin)

Four studies reported the use of whole plant cannabis products such as smoked herbal cannabis or resin. (Mashiah, 2012) reported at the Patients Out of Time Conference and is published on the Multidisciplinary Association for Psychedelic Studies website, and therefore is not peer reviewed. The report is of an open-label pilot study of ad hoc smoked cannabis with roughly 23% THC and <1% CBD, where participants were restricted to less than 100g/month. Twenty-nine Israeli military veterans who were diagnosed with PTSD using the DSM-IV-TR criteria were treated for about one year. Average CAPS scores decreased; however, there were no statistical tests conducted (see Table 1 for means). At the end of the study, all patients still met criteria for moderate to severe PTSD. Limitations include no placebo control and no blinding of the study. There was a high drop-out rate; 19 people dropped out of the study but for unclear reasons not disclosed by the report.

The study by Reznik (2012) is an abstract that was presented at the International Conferences on Integrative Medicine in 2011. As part of “routine care”, 167 adult patients with PTSD who applied to the Ministry of Health in order to obtain a license for “Medical Cannabis” were assessed in a naturalistic and observational manner. The group consisted of patients with ‘pure’ PTSD (25 patients), PTSD patients with clinical depression (43 patients) and patients suffering from PTSD/chronic pain comorbidity (88 patients). Patients were administered “medical cannabis” (sativa species; 20-25% THC), roughly 2-3g per day. The study administered the CAPS but did not report of the outcome, stating that some “positive changes in CAPS scores was observed.” The abstract suggests that the major improvement was in those with PTSD and/or pain/depression; however, we cannot draw any conclusion from this study, as no statistics were given.

Greer, Grob, and Halberstadt (2014) performed a retrospective chart-review which reported patients evaluated for the New Mexico Medical Cannabis program. New Mexico was the first state to list PTSD as a condition that medical cannabis could be prescribed for. Eighty participants were assessed using the CAPS; which saw a significant decrease in patients using cannabis in comparison to patients who did not use cannabis. Additionally, reductions were found in CAPS subscales for re-experiencing, avoidance-numbing, and hyper-arousal. Importantly, this is a self-selecting sample wherein the patients already knew that cannabis reduced their symptomology, and therefore entered the Medical Cannabis program. The study did not report the type of cannabis that was being used, and the screening occurred over the phone, where symptoms may have been exaggerated.

Finally, Passie, Emrich, Karst, Brandt, and Halpern (2012) conducted an observational clinical case report where in one individual (19 year old male with PTSD) “learned to smoke cannabis resin in order to cope with grave PTSD symptoms and who benefitted enormously from doing so”. Although in this study the patient was not administered cannabis, it was noted that the patient was using a 1:1 CBD:THC cannabis resin from Turkey, but no verification of this cannabinoid content is provided. The patient experienced reduced stress, fewer flashbacks, and decreased anxiety, but the potential for bias in this study precludes any strong conclusions being drawn about the use of cannabis for PTSD.

Discussion

In line with previous reviews, we found insufficient evidence to support the use of cannabinoids as a psychopharmacological treatment for PTSD. This lack of evidence is striking given the vast interest in cannabinoids as a treatment for PTSD and earlier repeated calls for RCTs (Kansagara et al., 2017; Loflin et al., 2017; O'Neil et al., 2017; Steenkamp et al., 2017). In comparison to previous narrative and systematic reviews, we used well-validated risk of bias and quality assessment tools that were appropriate for the study designs assessed (Higgins et al., 2016; Moher, 1998; Moher et al., 2009; Murad et al., 2018). Thus far, the evidence is comprised of small, low quality studies, with significant limitations to the study designs which make it difficult to draw a conclusion of their efficacy. Only 10 studies met our strict inclusion criteria: three investigations of the synthetic cannabinoid, nabilone, one investigation of oral THC, two investigations of CBD in oil and capsule form, and four investigations of smoked cannabis.

Specific limitations include, but are not limited to, small sample sizes, retrospective and poor-quality reporting, lack of matched control groups or a placebo arm and cross-sectional designs with short follow-up periods, lack of reporting on concomitant medications, and CUD. Even the primary double-blind placebo controlled clinical trial of nabilone (Jetly et al., 2015) had limitations to their study design, such as short follow up periods and small sample sizes. In the absence of RCTs, we also included the next best available levels of evidence (i.e. observational, retrospective studies and case reports) in this review. Existing studies are unable to provide evidence for the maintenance effects of the treatments since long-term follow-up studies have not been conducted. Whilst there is theoretical support, anecdotal support, and some experimental evidence that cannabinoids may be effective in treating PTSD and associated symptoms such as insomnia and nightmares, the evidence reviewed here does not support the use of cannabinoids for PTSD in routine clinical practice.

Despite the current low level of evidence, many states in the US allow cannabinoids for PTSD, which is accompanied by overwhelming demand by veterans who consider cannabis to be more effective and less complicated by side effects than alcohol and other psychopharmaceuticals (Elliott, Golub, Bennett, & Guarino, 2015). This is likely driven by a large unmet need for both psychotherapeutic and effective pharmacological interventions for this potentially highly debilitating disorder (Elliott et al., 2015). Where medications are currently prescribed, they often have limited efficacy (Krystal et al., 2011). Indeed, the harms and benefits of cannabinoids for PTSD should be weighed against each other in order to fully evaluate their use for this indication. The use of cannabinoids may cause severe side-effects in people with a history of psychosis (Cameron et al., 2014; Walsh et al., 2017), which is important to consider in combat veterans as high rates of hallucinations and/or delusions have been reported in this population, and is an indication of more severe psychopathology (Lindley, Carlson, & Sheikh, 2000). However, other side effects were relatively mild-to-moderate and included dry-mouth, feeling “stoned”, and stomach irritations, and these are considered less burdensome than the side-effects of currently prescribed drugs (Elliott et al., 2015).

There are warranted concerns around both safety and longer-term effects of medicinal cannabinoids. For example, cross-sectional research has shown that rates of CUDs are greater amongst PTSD populations in comparison to patients seeking cannabis without PTSD (Bohnert et al., 2014; Bonn-Miller et al., 2014). Recreational cannabis users with PTSD from a large sample of veterans with PTSD admitted to specialized VA treatment programs, showed poorer outcomes on severity of symptoms, violent behavior, and other drug use (Wilkinson et al., 2015). In regards to safety, there is evidence of a correlation between heavy cannabis use in teens and the development of psychosis (Mustonen et al., 2018) as well as an increase in emergency room visits (Hasin, 2018), and concerns around childhood exposures (Hasin, 2018). However, the use of illicit versus regulated cannabis for PTSD, and specific cannabinoids, that do not produce (e.g., CBD) have not been investigated in large cohort designs and further research is needed about harm reduction in these populations. Current ongoing RCT and non-RCT studies, which are expected to be completed in the United States by the end of 2019, should be able to add to the evidence regarding the clinical utility of cannabinoids for PTSD whilst addressing the side effect profile of different combinations of cannabinoids more adequately (O'Neil et al., 2017).

Sleep disturbances (i.e., nightmares, sleep avoidance, hyperarousal and insomnia) are clinically important symptoms of PTSD, such that over half of the studies included in this systematic review had sleep disturbances as an inclusion-criterion or was assessed an important outcome measure. There is concurrence in the studies included, alongside previous reviews (insert reviews) that medicinal cannabinoids can help with sleep disturbances. Understanding the mechanism underlying cannabis for sleep disturbances in PTSD is therefore imperative. Importantly, the use of cannabinoids may be more effective and with less risk of addiction in comparison to alternatives such as benzodiazepines or opiate-based medications, thereby providing a safer therapeutic alternative.

Future research

In addition to ongoing clinical trials of cannabinoids in PTSD, a range of further research is needed to fully understand and study cannabinoids as a potential treatment for PTSD. For example, understanding hippocampal mediated contextual learning disruptions in PTSD, and the effects of cannabinoids on these processes will help with further drug development. Investigating the role of CUD in maintaining PTSD will be important to weigh the harms versus benefits of medical cannabinoids. Importantly, an understanding of the effects of cannabinoids on the response to psychological interventions for PTSD and to other conventional pharmacotherapies (SSRIs and antipsychotics) will ensure evidence-based treatment plans. Additional research is required with cannabinoids in other types of trauma and with individuals from non-military backgrounds, including developmental trauma, and multiple complex traumata. Importantly, there is also high comorbidity in this population; over 90% will have at least one other lifetime psychiatric disorder (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), notably cannabis use disorder (CUD), alongside depression, alcohol use disorder, and anxiety-related disorders being the most prevalent (Kessler et al., 1995). Future research should address the effectiveness of treatments in ecologically valid samples with comorbid disorders. Also, it remains unknown whether eCB system dysfunction is a pre-existing risk factor to the development of PTSD, a consequence of trauma exposure, or an effect of persistent PTSD. Finally, large longitudinal cohort studies that investigate the co-occurrence of comorbidities within trauma populations are necessary. Increased interest and a more conducive research environment should be able to address these issues and facilitate more informed decision making in regards to cannabinoids for PTSD, including clinical prescription guidelines.

Strengths and Limitations

Strengths of this systematic review include a rigorous and pre-registered methodology with robust quality assessments. We used strict criteria for entry into the systematic review only including studies which utilized a psychometrically validated clinician rated or self-reported outcome measure such as the CAPS or the PCL. However, the major limitation of this study is the low level of evidence of the included studies, which impedes our ability to make clear conclusions from the data. Future clinical trials have already pre-registered their outcome measures (O'Neil et al., 2017) and should allow for the use of meta-analysis.

Conclusions

In conclusion, the clinical effectiveness of cannabinoids for the treatment of PTSD remains largely hypothetical; there is insufficient and poor-quality evidence of the effectiveness of cannabinoids for PTSD. This precludes any clinical recommendations about its use in routine clinical practice. Nonetheless, the clinical need is significant and despite the lack of evidence, cannabis can be obtained for medical reasons in some jurisdictions for this indication already. The lack of evidence poses a public health risk. Imminent RCTs will provide evidence for its utility. However, future research is also required to weigh up the harms and benefits of cannabis to inform policy making and clinical decision making in regards to individual patients.

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REFERENCES

Ballard, M. E., Bedi, G., & de Wit, H. (2012). Effects of delta-9-tetrahydrocannabinol on evaluation of emotional images. *Journal of Psychopharmacology, 26*(10), 1289-1298. doi:10.1177/0269881112446530

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

Bergamaschi, M. M., Queiroz, R. H. C., Zuardi, A. W., & Crippa, A. S. (2011). Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current Drug Safety, 6*(4), 237-249.

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., . . . McGuire, P. K. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology, 35*(3), 764-774. doi:10.1038/npp.2009.184

Bisogno, T., Hanuš, L., De Petrocellis, L., Tchilibon, S., Ponde, D. E., Brandi, I., . . . Di Marzo, V. (2001). Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British Journal of Pharmacology, 134*(4), 845-852.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress, 8*(1), 75-90.

Blanchard, E. B., Jones-Alexander, J., Buckley, T. C., & Forneris, C. A. (1996). Psychometric properties of the PTSD Checklist (PCL). *Journal of Behaviour Reseach Therapy, 34*(8), 669-673.

Bloomfield, M. A., Ashok, A. H., Volkow, N. D., & Howes, O. D. J. N. (2016). The effects of Δ 9-tetrahydrocannabinol on the dopamine system. *539*(7629), 369.

Bloomfield, M. A. P., Hindocha, C., Green, S. F., Wall, M. B., Lees, R., Petrilli, K., . . . Freeman, T. P. (2018). The neuropsychopharmacology of cannabis: A review of human imaging

studies. *Pharmacology and Therapeutics*. doi:https://doi.org/10.1016/j.pharmthera.2018.10.006
Boden, M. T., Babson, K. A., Vujanovic, A. A., Short, N. A., & Bonn-Miller, M. O. (2013). Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. *The American Journal on Addictions, 22*(3), 277-284.
Bohnert, K. M., Perron, B. E., Ashrafioun, L., Kleinberg, F., Jannausch, M., & Ilgen, M. A. (2014). Positive posttraumatic stress disorder screens among first-time medical cannabis patients: Prevalence and association with other substance use. *Addictive Behaviors, 39*(10), 1414-1417. doi:10.1016/j.addbeh.2014.05.022
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., Boden, M. T., Bucossi, M. M., & Babson, K. A. (2014). Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *The American Journal of Drug and Alcohol Abuse, 40*(1), 23-30.
Bonn-Miller, M. O., Loflin, M. J. E., Thomas, B. F., Marcu, J. P., Hyke, T., & Vandrey, R. (2017). Labeling accuracy of cannabidiol extracts sold online.. *JAMA, 318*(17), 1708-1709. doi:10.1001/jama.2017.11909
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. doi:10.1016/j.euroneuro.2013.06.009
Bremner, J. D., Krystal, J. H., Charney, D. S., & Southwick, S. M. (1996). Neural mechanisms in dissociative amnesia for childhood abuse. *The American Journal of Psychiatry, 153*(7), 71.
Bremner, J. D., Southwick, S. M., Darnell, A., & Charney, D. S. (1996). Chronic PTSD in Vietnam combat veterans: Course of illness and substance abuse. *American Journal of Psychiatry, 153*(3), 369-375. doi:10.1176/ajp.153.3.369
Brewin, C. (2001). Memory processes in post-traumatic stress disorder. *International Review of Psychiatry, 13*(3), 159-163.
Brewin, C. (2003). *Posttraumatic stress disorder: Malady or myth?* : Yale University Press.
Brewin, C., Cloitre, M., Hyland, P., Shevlin, M., Maercker, A., Bryant, R., . . . Reed, G. M. (2017). A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. *Clinical Psychology Review, 58*, 1-15. doi:10.1016/j.cpr.2017.09.001
Calignano, A., La Rana, G., Giuffrida, A., & Piomelli, D. (1998). Control of pain initiation by endogenous cannabinoids. *Nature, 394*(6690), 277.
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.
Campos, A. C., Moreira, F. A., Gomes, F. V., Del Bel, E. A., & Guimaraes, F. S. (2012). Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 367*(1607), 3364-3378. doi:10.1098/rstb.2011.0389
Carliner, H., Brown, Q. L., Sarvet, A. L., & Hasin, D. S. (2017). Cannabis use, attitudes, and legal status in the U.S.: A review. *Preventive Medicine, 104*, 13-23. doi:10.1016/j.ypmed.2017.07.008
Castillo, Pablo E., Younts, Thomas J., Chávez, Andrés E., & Hashimotodani, Y. (2012). Endocannabinoid signaling and synaptic function. *Neuron, 76*(1), 70-81. doiL10.1016/j.neuron.2012.09.020

Chan, G. C.-K., Hinds, T. R., Impey, S., & Storm, D. R. (1998). Hippocampal neurotoxicity of Δ9-tetrahydrocannabinol. *Journal of Neuroscience, 18*(14), 5322-5332.
Cohen, J. (1988). *Statistical power analysis for the social sciences (2nd Ed.)*. Hillsdale NJ: Lawrence Erlbaum Associates, Publishers.
Cougle, J. R., Bonn-Miller, M. O., Vujanovic, A. A., Zvolensky, M. J., Hawkins, K. A., J.R, C., . . . A., H. K. (2011). Posttraumatic stress disorder and cannabis use in a nationally representative sample. *Psychology of Addictive Behaviors, 25*(3), 554-558. doi:10.1037/a0023076
Cousijn, J., Núñez, A. E., & Filbey, F. M. (2018). Time to acknowledge the mixed effects of cannabis on health: a summary and critical review of the NASEM 2017 report on the health effects of cannabis and cannabinoids. *Addiction, 113*(5), 958-966.
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.
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.
Diamond, D. M., & Zoladz, P. R. (2016). Dysfunctional or hyperfunctional? The amygdala in posttraumatic stress disorder is the bull in the evolutionary China shop. *Journal of Neuroscience Research, 94*(6), 437-444. doi:10.1002/jnr.23684
Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy, 38*(4), 319-345.
Elliott, L., Golub, A., Bennett, A., & Guarino, H. (2015). PTSD and cannabis-related coping among recent veterans in New York City. *Contemporary Drug Problems, 42*(1), 60-76. doi:10.1177/0091450915570309
Elms, L., Shannon, S., Hughes, S., & Lewis, N. (2018). Cannabidiol in the treatment of post-traumaticstress disorder: A case series. *Journal of Alternative and Complementary Medicine*. doi:10.1089/acm.2018.0437
Elzinga, B. M., & Bremner, J. D. (2002). Are the neural substrates of memory the final common pathway in posttraumatic stress disorder (PTSD)? *Journal of Affective Disorders, 70*(1), 1-17. doi:10.1016/S0165-0327(01)00351-2
Etkin, A., & Wager, T. D. J. A. J. o. P. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry, 164*(10), 1476-1488. doi: 10.1176/appi.ajp.2007.07030504
Felder, C. C., Veluz, J. S., Williams, H. L., Briley, E. M., & Matsuda, L. A. (1992). Cannabinoid agonists stimulate both receptor- and non-receptor-mediated signal transduction pathways in cells transfected with and expressing cannabinoid receptor clones. *Molecular Pharmacology, 42*(5), 838-845.
Fraser, G. A. (2011). A preliminary look at the potential role of the endocannabinoid system in the management of PTSD. *Neurobiology of post-traumatic stress disorder.*, 331-344.
Freeman, T. P., Hindocha, C., Green, S. F., & Bloomfield, M. A. P. (2019). Medicinal use of cannabis based products and cannabinoids. *BMJ, 365*, l1141. doi:10.1136/bmj.l1141
Gorka, S. M., Fitzgerald, D. A., de Wit, H., & Phan, K. L. (2014). Cannabinoid modulation of amygdala subregion functional connectivity to social signals of threat. *International Journal of Neuropsychopharmacology, 18*(3). doi:10.1093/ijnp/pyu104
Gorka, S. M., Phan, K. L., Lyons, M., Mori, S., Angstadt, & Rabinak, C. A. (2015). Cannabinoid Modulation of Frontolimbic Activation and Connectivity During Volitional Regulation of Negative Affect. *Neuropsychopharmacology, 41*, 1888. doi:10.1038/npp.2015.359

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.
Hasin, D. S. J. N. (2018). US epidemiology of cannabis use and associated problems. *43*(1), 195.
Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America, 87*(5), 1932-1936.
Higgins, J., Sterne, J., Savović, J., Page, M., Hróbjartsson, A., Boutron, I., . . . Eldridge, S. (2016). *A revised tool for assessing risk of bias in randomized trials* (Vol. Issue 10 (Suppl 1).). Cochrane Database of Systematic Reviews.
Hill, M. N., Miller, G. E., Carrier, E. J., Gorzalka, B. B., & Hillard, C. J. (2009). Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. *Psychoneuroendocrinology, 34*(8), 1257-1262. doi:10.1016/j.psyneuen.2009.03.013
Hill, M. N., & Patel, S. (2013). Translational evidence for the involvement of the endocannabinoid system in stress-related psychiatric illnesses. *Biology of Mood & Anxiety Disorders, 3*(1), 19. doi:10.1186/2045-5380-3-19
Hillard, C. J., Weinlander, K. M., & Stuhr, K. L. (2012). Contributions of endocannabinoid signaling to psychiatric disorders in humans: Genetic and biochemical evidence. *Neuroscience, 204*, 207-229. doi:10.1016/j.neuroscience.2011.11.020
Hindocha, C., Freeman, T. P., Schafer, G., Gardener, C., Das, R. K., Morgan, C. J., & Curran, H. V. (2015). Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. *European Neuropsychopharmacology, 25*(3), 325-334. doi:10.1016/j.euroneuro.2014.11.014
Iffland, K., & Grotenhermen, F. (2017). An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. *Cannabis and Cannabinoid Research, 2*(1), 139-154. doi:10.1089/can.2016.0034
Jetly, R., Heber, A., Fraser, G., Boisvert, D., R, J., A, H., . . . D., B. (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. doi:10.1016/j.psyneuen.2014.11.002
Kansagara, D., O'Neil, M., Nugent, S., Freeman, M., Low, A., Kondo, K., . . . Paynter, R. (2017). Benefits and harms of cannabis in chronic pain or post-traumatic stress disorder: A systematic review.
Karam, E. G., Friedman, M. J., Hill, E. D., Kessler, R. C., McLaughlin, K. A., Petukhova, M., . . . Koenen, K. C. (2014). Cumulative traumas and risk thresholds: 12-month PTSD in the World Mental Health (WMH) surveys. *Depression and Anxiety, 31*(2), 130-142. doi:10.1002/da.22169
Kathmann, M., Flau, K., Redmer, A., Trankle, C., & Schlicker, E. (2006). Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn-Schmiedebergs Archives of Pharmacology, 372*(5), 354-361. doi:10.1007/s00210-006-0033-x
Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 52*(12), 1048-1060.
Krystal, J. H., Rosenheck, R. A., & Cramer, J. A. (2011). Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service–related PTSD: A randomized trial. *JAMA, 306*(5), 493-502. doi:10.1001/jama.2011.1080

Laprairie, R. B., Bagher, A. M., Kelly, M. E. M., & Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB(1) receptor. *British Journal of Pharmacology, 172*(20), 4790-4805. doi:10.1111/bph.13250

LeDoux, J. (2007). The amygdala. *Current Biology, 17*(20), R868-R874.

Legislature, N. C. o. S. (2019). Marijuana Overview Retrieved from http://www.ncsl.org/research/civil-and-criminal-justice/marijuana-overview.aspx

Lindley, S. E., Carlson, E., & Sheikh, J. (2000). Psychotic symptoms in posttraumatic stress disorder. *CNS Spectrums, 5*(9), 52-57. doi:
10.1017/S1092852900021659

Loflin, M., Babson, K. A., & Bonn-Miller, M. O. (2017). Cannabinoids as therapeutic for PTSD. *Current Opinion in Psychology, 14*, 78-83. doi:10.1016/j.copsyc.2016.12.001

Loflin, M., Earleywine, M., & Bonn-Miller, M. (2017). Medicinal versus recreational cannabis use: Patterns of cannabis use, alcohol use, and cued-arousal among veterans who screen positive for PTSD. *Addictive Behaviors, 68*, 18-23. doi:10.1016/j.addbeh.2017.01.008

Mashiah, M. (2012). *Medical cannabis as treatment for chronic combat PTSD: promising results in an open pilot study.* Paper presented at the Patients Out of Time Conference.

Metrik, J., Bassett, S. S., Aston, E. R., Jackson, K. M., & Borsari, B. (2018). Medicinal versus recreational cannabis use among returning veterans. *Translational Issues in Psychological Science, 4*(1), 6-20. doi:10.1037/tps0000133

Moher, D. (1998). CONSORT: An evolving tool to help improve the quality of reports of randomized controlled trials. Consolidated Standards of Reporting Trials. *JAMA, 279*, 1489-1491. doi:10.1001/jama.279.18.1489

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS One, 6*(7), e10000097. doi: 10.1371/
journal.pmed.1000097

Morena, M., Patel, S., Bains, J. S., & Hill, M. N. (2016). Neurobiological interactions between stress and the endocannabinoid system. *Neuropsychopharmacology, 41*(1), 80.

Murad, M. H., Sultan, S., Haffar, S., & Bazerbachi, F. (2018). Methodological quality and synthesis of case series and case reports. *BMJ Evidence Based Medicine, 23*(2), 60-63. doi:10.1136/bmjebm-2017-110853

Mustonen, A., Niemelä, S., Nordström, T., Murray, G. K., Mäki, P., Jääskeläinen, E., & Miettunen, J. (2018). Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. *The British Journal of Psychiatry, 212*(4), 227-233. doi:10.1192/bjp.2017.52

National Academies of Sciences, E., & Medicine. (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*: National Academies Press.

Neumeister, A., Normandin, M. D., Pietrzak, R. H., Piomelli, D., Zheng, M. Q., Gujarro-Anton, A., . . . Huang, Y. (2013). Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: A positron emission tomography study. *Molecular Psychiatry, 18*(9), 1034-1040. doi:10.1038/mp.2013.61

Neumeister, A., Normandin, M. D., Pietrzak, R. H., Piomelli, D., Zheng, M. Q., Gujarro-Anton, A., . . . Y., H. (2013). Elevated brain cannabinoid CB 1 receptor availability in post-traumatic stress disorder: A positron emission tomography study. *Molecular Psychiatry, 18*(9), 1034-1040. doi:10.1038/mp.2013.61

NICE. (2018). Post Traumatic Stress Disorder (NICE guideline [NG116]).

O'Neil, M. E., Nugent, S. M., Morasco, B. J., Freeman, M., Low, A., Kondo, K., . . . D., K. (2017). Benefits and harms of plant-based cannabis for posttraumatic stress disorder a systematic review. *Annals of Internal Medicine, 167*(5), 332-340. doi:

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. doi:10.1002/dta.1377

Pertwee, R. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. *British Journal of Pharmacology, 153*(2), 199-215.

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. doi:10.1523/jneurosci.5603-07.2008

Phillips, B., Ball, C., Badenoch, D., Straus, S., Haynes, B., & Dawes, M. J. B. i. (2011). Oxford centre for evidence-based medicine levels of evidence (May 2001). *107*(5), 870.

Pietrzak, R. H., Huang, Y., Corsi-Travali, S., Zheng, M.-Q., Lin, S.-f., Henry, S., . . . Neumeister, A. (2014). Cannabinoid type 1 receptor availability in the amygdala mediates threat processing in trauma survivors. *Neuropsychopharmacology39*(11), 2519-2528. doi:10.1038/npp.2014.110

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. *Journal of Neuropharmacology, 64*, 396-402.

Reznik, I. (2012). Post-traumatic stress disorder and medical cannabis use: A naturalistic observational study. *European Neuropsychopharmacology, 22*(SUPPL. 2), S363-S364.

Richardson, L. K., Frueh, B. C., & Acierno, R. (2010). Prevalence estimates of combat-related post-traumatic stress disorder: Critical review. *Australian New Zealand Journal of Psychiatry, 44*(1), 4-19.

Rodriguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F. J., Bilbao, A., Cippitelli, A., & Navarro, M. (2004). The endocannabinoid system: Physiology and pharmacology. *Alcohol and Alcoholism, 40*(1), 2-14.

Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, open-label, pilot study of add-on oral Δ 9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation, 34*(8), 587-591. doi:10.1007/s40261-014-0212-3

Ruehle, S., Rey, A. A., Remmers, F., & Lutz, B. (2012). The endocannabinoid system in anxiety, fear memory and habituation. *Journal of Psychopharmacology, 26*(1), 23-39. doi:10.1177/0269881111408958

Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical Hypotheses, 66*(2), 234-246. doi:10.1016/j.mehy.2005.08.026

Russo, E. B., Burnett, A., Hall, B., & Parker, K. K. (2005). Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochemical Research, 30*(8), 1037-1043.

Ryberg, E., Larsson, N., Sjogren, S., Hjorth, S., Hermansson, N. O., Leonova, J., . . . Greasley, P. J. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. *British Journal ofPharmacology, 152*(7), 1092-1101. doi:10.1038/sj.bjp.0707460

Seeman, P. (2016). Cannabidiol is a partial agonist at dopamine D2High receptors, predicting its antipsychotic clinical dose. *Translational Psychiatry, 6*, e920. doi:10.1038/tp.2016.195

Shannon, S., & Opila-Lehman, J. (2016). Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: A case report. *The Permanente Journal, 20*(4), 108.

Steenkamp, M. M., Blessing, E. M., Galatzer-Levy, I. R., Hollahan, L. C., Anderson, W. T., M.M, S., . . . T., A. W. (2017). Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: A literature review. *Depression and Anxiety, 34*(3), 207-216. doi:10.1002/da.22596

Straiker, A., Dvorakova, M., Zimmowitch, A., & Mackie, K. P. (2018). Cannabidiol inhibits endocannabinoid signaling in autaptic hippocampal neurons. *Molecular Pharmacology*. doi:10.1124/mol.118.111864

Trezza, V., & Campolongo, P. (2013). The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). *Frontiers in Behavioral Neuroscience, 7*, 1-5. doi:10.3389/fnbeh.2013.00100

Vandrey, R., Raber, J. C., Raber, M. E., Douglass, B., Miller, C., & Bonn-Miller, M. O. (2015). Cannabinoid dose and label accuracy in edible medical cannabis products. *JAMA, 313*(24), 2491-2493. doi:10.1001/jama.2015.6613

Viveros, M., Marco, E. M., & File, S. E. (2005). Endocannabinoid system and stress and anxiety responses. *Pharmacology Biochemistry and Behavior, 81*(2), 331-342. doi: 10.1016/j.pbb.2005.01.029

Volkow, N. D., Hampson, A. J., & Baler, R. D. (2017). Don't worry, be happy: Endocannabinoids and cannabis at the intersection of stress and reward. *Annual Review of Pharmacology and Toxicology, 57*, 285-308.

Walsh, Z., Gonzalez, R., Crosby, K., M, S. T., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. *Clinical Psychology Review, 51*, 15-29. doi:10.1016/j.cpr.2016.10.002

Wilkinson, S. T., Radhakrishnan, R., D'Souza, D. C. (2016). A systematic review of the evidence for medical marijuana in psychiatric indications. *Journal of Clinical Psychiatry, 77*(8), 1050-1064. doi:10.4088/JCP.15r10036

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. doi:

Woodhams, S. G., Sagar, D. R., Burston, J. J., & Chapman, V. (2015). The role of the endocannabinoid system in pain. In *Pain control* (pp. 119-143): Springer.

Yehuda, R., & LeDoux, J. (2007). Response variation following trauma: A translational neuroscience approach to understanding PTSD. *Neuron, 56*(1), 19-32.

Zoladz, P. R., & Diamond, D. (2016). Predator-based psychosocial stress animal model of PTSD: Preclinical assessment of traumatic stress at cognitive, hormonal, pharmacological, cardiovascular and epigenetic levels of analysis. *Experimental Neurology, 284*, 211-219.

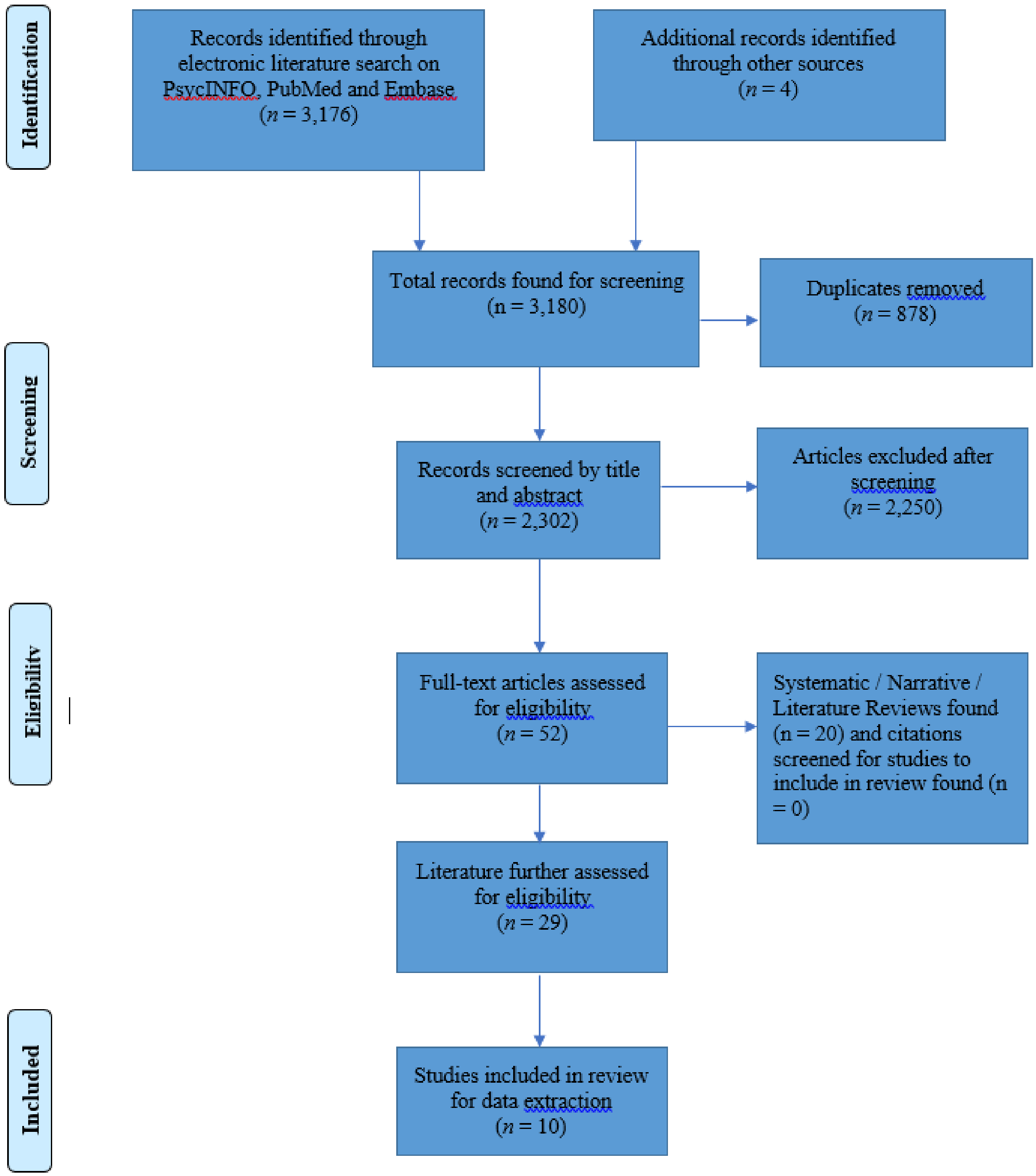

Figure 1. PRISMA flowchart.

TABLE 1: Studies of the effects of cannabinoids on PTSD symptomology, ordered by level of evidence and type of cannabinoid drug.

	Drug / dose / route of administration	Type of study	PTSD diagnosis / additional inclusion criteria	Length of treatment	Participants n	Level of evidence*	Primary outcome measures	Primary outcome result	Secondary Outcomes	Secondary outcome results	Adverse Effects (AE)
					Nabilone						
Jetly et al. 2015 DOI:10.1016/j.psyneuen.2014.11.002	Nabilone 500 micrograms to 3.0 mg Nabilone or placebo Oral	Pilot randomized, double-blind, placebo-controlled crossover clinical trial	PTSD (DSM-IV-TR) via CAPS CAPS score distressing dreams and difficulty sleeping ≥ 5 the week before entering trial Operational index trauma > 2 years before screening for study	16 weeks	10	2b	NR	NR	CAPS Recurring and Distressing Dream scores	CAPS reduced. Nabilone: -3.6 ± 2.4. Placebo: 1.0 ± 2.1, *p* = .03, *d* = 1.15)	No drop outs due to AEs reported. No severe AEs. AEs in 50% in Nabilone group and 60% in the placebo group. Dry mouth. Headache (*n* = 6 in Nabilone group, *n* = 4 in placebo group)
									CAPS Difficulty Falling and Staying Asleep scores	No effect observed on sleep quality	
									WBQ	WBQ improved: Nabilone: 20.8 ± 22 Placebo: 0.4 ± 20.6, *p* = .04, *d* = 0.99).	
									CGI-C	CGI-C improved. Nabilone: 1.9 ± 1.1 (i.e. much improved). Placebo: 3.2 ± 1.2 (i.e. minimally improved), *p* = 0.05, *d* = 1.13	
Cameron et al. 2014 DOI:10.1097/JCP.0000000000000180	Nabilone 1,4 mg mean initial daily dosage (range 200 micrograms - 2.0 mg). 4.0 mg mean final dosage. Daily. Of *n* = 17 participants on Nabilone for ≥20 weeks dosage	Retrospective chart review	Clinical PTSD (DSM-IV-TR)	Mean 11.2 weeks (Range 1 day – 36 weeks)	104	2c	PCL-C total	Significant reduction in PCL-C scores (*n* = 58) pre-drug: 54.7 (13.0) post-drug: 38.8 (7.1) *p* = .001, *d* = 1.52	Number of hours slept	Increase in number of hours slept. Pre-drug: 5.0 (1.4) to post-drug: 7.2 (1.2), *p* < .001, *d* = 1.69	31 subjects reported AEs, 10 dropped out. Psychosis was the most serious AE (2 subjects) – both had pre-existing psychotic illness. Side-effects: sedation, 12.5%; dry
									Number of nights with nightmares / week	Reduction in number of nights with nightmares/ week *n* = 90 from Pre-drug: 5.2 (2.2) to post-drug 0.9 (1.8), *p* < .001, *d* = 2.14	
									GAF	GAF scores increased pre-drug: 45 (6.9) to post-drug 58.2 (8.4) *p* = .001, *d* = 1.72	

	increased to 4.6 mg Powder form in water or as oral capsule								Chronic pain	61/68 reported subjective improvement in pain (no statistics)	mouth, 6.7%; feeling ‘‘stoned,’’ 3.8%; orthostatic hypotension, 1.9%; agitation, 1.9%; headache, 1.0%.
Fraser, 2009 DOI:10.1111/j.1755-5949.2008.00071.x	Nabilone Started 500 micrograms, dose adjusted according to response, 1 hour prior to bedtime. Effective dose range: 200 micrograms to 4.0 mg. Oral	Open label Clinical Trial. Chart review	PTSD (DSM – IV-TR) via PTSD Diagnosis Scale Nightmare frequency was required to be a minimum of once weekly	4-12 months	47	3b	NR	NR	Intensity of nightmares (1 to 5)	No statistics 34 patients (72%) experienced total cessation or lessening of severity of nightmares, 28 patients had total cessation of nightmares and 6 had satisfactory reduction.	13 patients (28%) experienced mild-to-moderate side effects shortly following nabilone initiation. light-headedness, forgetfulness, dizziness, and headache reported.
									Number of hours of sleep.	“Improvement in sleep time, reduction of daytime flashbacks, no longer experienced night sweats”	
					THC						
Roitman et al. 2014 DOI:10.1007/s40261-	THC 5 mg THC	Pilot, Open label Study	PTSD (DSM-IV) via CAPS Inclusion: Chronic PTSD	3 weeks	10	3b	CAPS total	CAPS total score: Start: 94 (13.42)	CAPS Intrusion	CAPS intrusion score Start: 24.2 (7.75) 3w: 18.7 (7.97) *p* >0.01, *d*= 0.7	Side effects reported in four cases (40%); dry mouth in

014-0212-3	Adjusted doses depending on severity of symptoms. Twice a day, SL	diagnosed more than 1yr before entering study and at least 3 years after trauma exposure		3 weeks 78 (23.6), *p* < .01, *d* = 0.83	CAPS Avoidance	CAPS avoidance score Start:37.5 (6.36) 3w: 35.0 (6.36) *p*> 0.05, *d* = 0.39	two patients (20%), headache in one patient (10%), and dizziness in another patient (10%).
					CAPS Arousal	CAPS arousal score Start: 32.3 (4.73) 24.3 (9.11) *p* < .02, *d* = 1.10	
					CGI - S	CGI – S Start: 6.0 (0.47) 3 weeks: 4.9 (0.99), *p* < .02 *d* = 1.42	No treatment discontinuations during the trial.
					GCI-I	CGI – I Start: 3.6 (0.52) 3 weeks: 2.7 (1.25), *p* < .03, *d* = 0.84	
					PSQI	PSQI score Start: 17.2 (2.65) 3 weeks: 13.9 (4.48), *p* < .05, *d* = 0.90	
					NFQ	NFQ nights frequency Start: 0.6 (0.3) 3 weeks 0.37 (0.33), *p* = .02, *d* = 0.41 NFQ frequency of nightmares Start: 0.81 (0.55) 3 weeks: 0.44 (0.41) *p*<0.04, *d* =0.76	
					NES	NES Start: 32.2 (11.29) 3weeks: 22.9 (8.7), *p* < .002, *d* = 0.92	

									Blood pressure, heart rate, weight and BMI.	No changes in blood pressure, weight, BMI or pulse	
Cannabidiol (CBD)											
Elms et al. 2018 DOI:10.1089/acm.2018.0437	CBD Oil Mean initial dose = 33.18 mg (SD: 23.34). Mean final dose was 48.64 mg (range 2-100) - Flexible dosing regimen Oral capsule or liquid spray	Retrospective Case series Open label	PTSD PCL-5 score > 33	8 weeks	11	2c	PCL–5	PCL-5 score n = 8 Baseline: 51.82 (9.13) 8 weeks 37.14 (14.38) *p* value not reported. *d* = 1.219	NR	NR	No drop-outs Fatigue: 2 patients. Daytime fogginess and impaired concentration: 1 patient gastrointestinal bloating or pain: 2 patients (1 of these patients had pre-existing inflammatory bowel syndrome and anorexia)
Shannon et al. 2016 DOI:10.7812/TPP/16-005	CBD 25 mg plus 6-12 mg SL spray as needed depending on worsening of symptoms Oral Capsule	Case report of a 10 year old girl	PTSD	6 months	1	3b	NR	NR	Sleep scale SCARED	Sleep scale score decreased from 59 to 38 in 7 months SCARED score reduced from 34 to 18 in 7 months	No side effects reported
Cannabis Preparations											

Mashiah 2012 No DOI. Presented findings at Patients Out of Time Conference https://bit.ly/2tPOTPB	Herbal cannabis of roughly 23% THC and <1% CBD. no greater than 100 g/month Smoked	Open label pilot study	Clinical PTSD (DSM-IV-TR) combat veterans	< 11.3 +/- 2.9 months	29	4	CAPS	Total CAPS reduced baseline: 97.7 +/- 13.3 Final CAPS assessment 53.7 +/- 18.3	Self assessed QOL A clinician-assessment of clinical improvement	NR	19 patients dropped out. Reason not given.
Reznik, 2011 DOI:10.1016/S0924-977X(12)70563-1	Herbal cannabis sativa species containing 20-25% THC Daily dosage range 2-3 gr/day Smoked	Naturalistic observational study	Patients had applied to the Ministry of Health to obtain a Medical Cannabis licence. No specific measure used to determine PTSD diagnosis	3 years	167	4	CAPS	NR	QOLS CGI-I Pain scores	NR	NR
Greer et al. 2014 DOI:10.1080/02791072.2013.873843	Herbal cannabis Various	Retrospective case study	Self-reported PTSD (DSM-IV) determined by telephone screening	2.5 years	80	4	Total CAPS score	Reduction of total CAPS scores cannabis: 22.5 (16.9) no cannabis: 98.8 (17.6) $p < .0001$; $d = 4.42$	CAPS re-experiencing cluster	CAPS re-experiencing cluster decreased under cannabis From 29.5 (6.4) to 7.3 (5.9), $p < .0001$, $d = 3.61$	NR
									CAPS numbing and avoidance	CAPS numbing and avoidance decreased from 38.2 (8.4) to 8.7 (8.0) under cannabis, $p < .0001$, $d = 3.596$	
									CAPS hyperarousal	CAPS hyperarousal decreased from 31 (6.2) to 6.6 (6.0) $p < .0001$, $d = 4.00$	

Passie et al. 2012 DOI:10.1002/dta.1377	Cannabis Resin (CBD + THC) 50:50 Smoked in a joint	Observational Clinical Case Study	Diagnosis of PTSD (not stated how diagnosed)	6 months	1	4	NR	NR	NR	No statistics. Subjective reduction in dissociative episodes associated with re-experiencing phenomena Increased subjective cognitive control. Increased subjective compartmentalization from trauma memories as if on 'inner screen' from a distance.	No side effects

TABLE 1: Studies of the Effects of Cannabinoids on PTSD Symptomology, Ordered by Level of Evidence and Type of Cannabinoid Drug.

Note. AE = adverse events; BMI = Body Mass Index; CAPS = Clinician-Administered PTSD scale; CBD = Cannabidiol; CGI – C = Clinical global impression – Change; CGI – I = Clinical global impression – Improvement; CGI – S = Clinical global impression – Severity; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GAF = Global Assessment of Functioning; NES = Nightmare Effects Survey; NFQ = Nightmare Frequency Questionnaire, NR = Not reported; PCL-C = Posttraumatic Checklist-Civilian Version; PSQI = Pittsburg Sleep Quality Index; THC = delta-9-tetrahydrocannabinol; SCARED = Screen for Anxiety Related Disorders; SL = sublingual; QOL= Quality of Life; WBQ = Well-being questionnaire

*Oxford Centre for Evidence-based Medicine – Levels of Evidence guideline

Study	1) Random sequence generation	2) Allocation concealment	3) Blinding of participants and personnel	4) Blinding of outcome assessments	5) Incomplete outcome data	6) Selective reporting	7) Other bias
Jetly et al. 2015	Green	Green	Green	Green	Green	Green	Yellow
Cameron et al. 2014	Red	Red	Red	Red	Green	Green	Red
Fraser, 2009	Red	Yellow	Red	Red	Red	Red	Yellow
Roitman et al. 2014	Red	Red	Red	Red	Green	Green	Red
Elms et al. 2018	Red	Red	Red	Red	Green	Green	Red
Mashiah, 2012	Red	Red	Red	Red	Red	Red	Red
Shannon et al. 2016	Red	Red	Red	Red	Red	Red	Yellow
Reznik, 2011	Red	Red	Red	Red	Red	Red	Red
Greer et al. 2014	Red	Red	Red	Red	Green	Green	Red
Passie et al. 2012	Red	Red	Red	Red	Red	Red	Red

TABLE 2. Risk of Bias Assessment in Each Study
Note. Green = low risk; Yellow = unclear risk; Red = high risk.

Table 3: CONSORT Table for Pilot and Feasibility Trials

	Jetly et al 2015	**Cameron et al 2014**	**Fraser 2009**	**Roitman et al 2014**	**Mashiah 2012**	**Reznik 2011**
1a Identification as randomized in the title						
1b Structured summary of study design, methods, results, and conclusions						
2a Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial						
2b Specific objectives or research questions for pilot trial						
3a Description of pilot trial design including allocation ratio						
3b Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons						
4a Eligibility criteria for participants						
4b Settings and locations where the data were collected						
4c How participants were identified and consented						
5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered						
6a Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed						
6b Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons						
6c If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial						
7a Rationale for numbers in the pilot trial						
7b When applicable, explanation of any interim analyses and stopping guidelines						
8a Method used to generate the random allocation sequence						

8b Type of randomisation(s); details of any restriction (such as blocking and block size)						
9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned						
10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions						
11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how						
11b If relevant, description of the similarity of interventions						
12 Methods used to address each pilot trial objective whether qualitative or quantitative						
13a For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective						
13b For each group, losses and exclusions after randomisation, together with reasons						
14a Dates defining the periods of recruitment and follow-up						
14b Why the pilot trial ended or was stopped						
15 A table showing baseline demographic and clinical characteristics for each group						
16 For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group						
17 For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group						

18 Results of any other analyses performed that could be used to inform the future definitive trial						
19 All important harms or unintended effects in each group						
19a If relevant, other important unintended consequences						
20 Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility						
21Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies						
22a Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence						
22a Implications for progression from pilot to future definitive trial, including any proposed amendments						
23 Registration number for pilot trial and name of trial registry						
24 Where pilot trial protocol can be accessed, if available						
25 Sources of funding and other support (such as supply of drugs), role of funders						
26 Ethical approval or approval by research review committee, confirmed with reference number						

Note. Green = present; Red = absent; Yellow = unclear; Grey = not applicable.

Table 4. Methodological Quality Assessment for Case Reports/Case Series

	Elms et al. 2018	Shannon et al. 2016	Greer et al. 2014	Passie et al. 2012
1) Clear selection method?				
2) Exposure adequately ascertained?				
3) Outcome adequately ascertained?				
4) Alternative causes ruled out?				
5) Challenge/rechallenge phenomenon?				
6) Dose-response effect?				
7) Follow up long enough?				
8) Sufficient reporting?				

Note. Green = low potential bias; Red = high potential bias.