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

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ABSTRACT

Objectives: Posttraumatic 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 had PTSD diagnosed 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 symptomology 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.

PROSPERO registration number: 121646

KEYWORDS

Cannabis; THC; CBD; nabilone; posttraumatic stress disorder; treatments

Posttraumatic stress disorder (PTSD)

PTSD is a potentially debilitating condition. PTSD affects approximately 1% of the population (Karam et al., 2014) and is overrepresented in military veterans (Richardson, Frueh, & Acierno, 2010). The fundamental features of PTSD include (1) reexperiencing of the trauma through intrusive memories, flashbacks, and/or nightmares; (2) active avoidance of external and internal reminders of the trauma; and (3) hyperarousal (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 reprocessing and reappraisal 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 suboptimal 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...
Cannabis and cannabinoids

Cannabinoids act on the endogenous cannabinoid system (endocannabinoid system; eCB system), a neuro-modulatory system that 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 of endogenous ligands (anandamide and 2-arachidonoylglycerol [2-AG]), cannabinoid receptors (type 1 [CB1R] and type 2 [CB2R]), and enzymes that catabolize the internal ligands (fatty acid amide hydrolase and [FAAH] and monoacylglycerol lipase). Activation of CB1R, the most abundant class of G-protein coupled receptors in the central nervous system (Pertwee, 2008), suppresses neurotransmitter release. CB1Rs 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 and 2-AG) are released “on demand” from the postsynaptic 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 Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Pertwee, 2008). THC is the primary psychoactive cannabinoid found in cannabis. CBD is nonintoxicating, has anxiolytic and antipsychotic properties, and has a superior tolerability and side-effect profile in comparison to the CB1R agonists which include THC, nabilone, and dronabinol (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Iffland & Grotenhermen, 2017). Strains of cannabis may be differentially therapeutic due to variance in cannabinoid content, with high-THC strains producing 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 that 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 U.S. 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 CB1R 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 CB1R (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015). Regarding the eCB system, CBD likely acts through negative allosteric modulation of the CB1R and FAAH inhibition (Laprairie et al., 2015; Straiker, Dvorakova, Zimmowitch, & Mackie, 2018). CBD modulates 5-HT1A (Russo, Burnett, Hall, & Parker, 2005), GPR55 (Ryberg et al., 2009), the μ- and δ-opioid receptors (Kathmann, Flau, Redmer, Trankle, & Schlicker, 2006), the transient receptor potential cation channel V1 (Bisogno et al., 2001), peroxisome proliferator-activated receptor gamma (Campos, Moreira, Gomes, Del Bel, & Guimarães, 2012), and dopamine D₂ receptors (Seeman, 2016).

Among 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 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 U.S. cannabis dispensaries suggest that cannabinoids may help with PTSD-associated traumatic intrusions, hyperarousal, 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 that the eCB system is involved in the pathophysiology of PTSD given its key role for 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 hyperreactivity, which contributes to the state of constant vigilance seen in patients with PTSD (Etkin & Wager, 2007; LeDoux, 2007; Yehuda & LeDoux, 2007). Excessive amygdala hyperreactivity is likely to contribute to many PTSD symptoms (for a review, see Diamond & Zoladz, 2016; Zoladz & Diamond, 2016), including preventing reintegration of trauma memories (Ehlers & Clark, 2000). CB1Rs, upon which THC acts, are highly expressed within the amygdala (Herkenham et al., 1990). Amygdalar CB1R availability specifically was related to attentional bias to threat, a key symptom in PTSD (Pietrzak et al., 2014).

Borne out of a large preclinical literature base that suggested that cannabinoids were modulating emotional memory, fear, and anxiety (Ruehl 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 that 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). CB1Rs are densely expressed in the hippocampus (Chan, Hinds, Impey, & Storm, 1998). A positron emission topography study found elevated CB1R 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
Methods

The following procedures were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1; Moher, 1998; Moher, Liberati, Tetzlaff, Altman, & PRISMA 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, and Embase. We searched these databases using the OVID interface to find relevant studies. This search was conducted on December 10, 2018, and completed on December 15, 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 cannabinoid OR THC OR tetrahydrocannabinol* 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 as follows: (1) The patient has had PTSD diagnosed using the Diagnostic and Statistical Manual (DSM) or the International Classification of Diseases and/or via a validated clinician-administered PTSD psychometric symptom scale (such as the Clinician-Administered PTSD Scale [CAPS]) or patient-rated measures such as the PTSD Checklist (PCL) and (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 the following: (1) studies not in English and (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 CAPS (Blake et al., 1995) and 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 well-being 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 Center 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; and (12) adverse effects.

**Risk of bias assessment (Table 2)**

We assessed risk of bias using the Cochrane Risk of Bias tool for RCTs, as recommended by the Cochrane Collaboration (Higgins et al., 2016). The eligible studies were assessed against seven key criteria, which were (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 comprises a checklist of 25 items that focus on how trials were designed, analyzed, and interpreted (see Table 3). Also, an eight-item checklist (Murad, Sultan, Haffar, & Bazerbachi, 2018) covering selection, ascertainment, causality, and reporting domains was
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/dose/route of administration</th>
<th>Type of study</th>
<th>PTSD diagnosis/additional inclusion criteria</th>
<th>Length of treatment</th>
<th>Participants</th>
<th>Level of evidence</th>
<th>Primary outcome measures</th>
<th>Primary outcome result</th>
<th>Secondary outcomes</th>
<th>Secondary outcome results</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabilone</td>
<td>Jery et al. 2015 DOI:10.1001/jjspynen.2014.11.002</td>
<td>Pilot randomized, double-blind, placebo-controlled crossover clinical trial</td>
<td>PTSD (DSM IV–TR) via CAPS</td>
<td>16 weeks</td>
<td>10</td>
<td>2b</td>
<td>NR</td>
<td>NR</td>
<td>CAPS Recurring and Distressing Dream scores</td>
<td>Nabilone: 36 ± 2.4</td>
<td>Placebo: 16 ± 2.1</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Cameron et al. 2014 DOI:10.1016/j.jpsychres.2014.11.002</td>
<td>Retrospective chart review</td>
<td>Clinical PTSD (DSM IV–TR)</td>
<td>Mean 11.2 weeks (Range 1 day– 36 weeks)</td>
<td>104</td>
<td>2c</td>
<td>PCL-C total</td>
<td>Number of hours slept</td>
<td>Significant reduction in PCL-C scores (n = 58)</td>
<td>Predrug: 54.7 (13.0)</td>
<td>Postdrug: 38.8 (7.1)</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Cameron et al. 2014 DOI:10.1001/jcp.0000000000000180</td>
<td>Open label clinical Trial</td>
<td>PTSD (DSM – IVTR) via PTSD Diagnosis Scale</td>
<td>4–12 months</td>
<td>47</td>
<td>3b</td>
<td>NR</td>
<td>NR</td>
<td>Intensity of nightmares (1 to 5)</td>
<td>No subjective subjective improvement in pain (no statistics)</td>
<td>No statistics</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Fraser, 2009 DOI:10.1111/j.1558-3358.2008.00071.x</td>
<td>Pilot, open-label study</td>
<td>PTSD (DSM–IV TR) via CAPS</td>
<td>3 weeks</td>
<td>10</td>
<td>2b</td>
<td>CAPS total</td>
<td>CAPS total score</td>
<td>Start: 94 (13.42) 3 weeks: 78 (23.6)</td>
<td>p &lt; .01, d = 0.83</td>
<td>No treatment discontinuations</td>
</tr>
<tr>
<td>THC</td>
<td>Roitman et al. 2014 DOI:10.1007/s40261-014-0212-3</td>
<td>Pilot, open-label study</td>
<td>PTSD (DSM–IV TR) via CAPS</td>
<td>3 weeks</td>
<td>10</td>
<td>3b</td>
<td>CAPS total</td>
<td>CAPS Intrusion</td>
<td>Start: 34.2 (7.75) 3 weeks: 18.7 (7.97)</td>
<td>p &lt; .01, d = 0.73</td>
<td>No treatment discontinuations during the trial</td>
</tr>
<tr>
<td>THC</td>
<td>Pastore et al. 2013 DOI:10.1007/s40261-015-0283-z</td>
<td>Open label study</td>
<td>PTSD (DSM–IV TR) via CAPS</td>
<td>8 weeks</td>
<td>20</td>
<td>2b</td>
<td>CAPS total</td>
<td>CAPS total score</td>
<td>Start: 56.2 (9.0) 8 weeks: 43.3 (12.6)</td>
<td>p &lt; .01, d = 0.83</td>
<td>No treatment discontinuations during the trial</td>
</tr>
<tr>
<td>THC</td>
<td>Pastore et al. 2013 DOI:10.1007/s40261-015-0283-z</td>
<td>Pilot, open-label study</td>
<td>PTSD (DSM–IV TR) via CAPS</td>
<td>8 weeks</td>
<td>20</td>
<td>2b</td>
<td>CAPS total</td>
<td>CAPS total score</td>
<td>Start: 56.2 (9.0) 8 weeks: 43.3 (12.6)</td>
<td>p &lt; .01, d = 0.83</td>
<td>No treatment discontinuations during the trial</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/dose/route of administration</th>
<th>Type of study</th>
<th>PTSD diagnosis/additional inclusion criteria</th>
<th>Length of treatment</th>
<th>Participants</th>
<th>Level of evidence*</th>
<th>Primary outcome measures</th>
<th>Primary outcome result</th>
<th>Secondary outcomes</th>
<th>Secondary outcome results</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANNABIDIOL (CBD)</td>
<td>Elms et al. 2018</td>
<td>CBD Oil</td>
<td>Mean initial dose = 33.18 mg (SD = 23.34)</td>
<td>4 weeks</td>
<td>11</td>
<td>2c</td>
<td>PCL–5 score &gt; 33</td>
<td>CGI-I &lt;br&gt; Start: 36 (0.52)</td>
<td>3 weeks: 27 (1.25)</td>
<td>p &lt; .01, d = 0.84</td>
<td></td>
</tr>
<tr>
<td>CANNABIS PREPARATIONS</td>
<td>Mashiah 2012</td>
<td>Herbal cannabis of roughly 25% THC and &lt; 1% CBD</td>
<td>Open label pilot study</td>
<td>Clinical PTSD (DSM-IV-TR) combat veterans</td>
<td>&lt; 11.3 ± 2.9 months</td>
<td>29</td>
<td>4</td>
<td>CAPS Total score</td>
<td>Reduction of total CAPS scores</td>
<td>No dropouts</td>
<td></td>
</tr>
<tr>
<td>REznik, 2012</td>
<td>Herbal cannabis sativa species containing 20%-25% THC</td>
<td>Naturalistic, observational study</td>
<td>Patients had applied to the Ministry of Health to obtain a medical cannabis license; no specific measure used to determine PTSD diagnosis</td>
<td>3 years</td>
<td>167</td>
<td>4</td>
<td>CAPS Self assessed QOL</td>
<td>No dropouts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greer et al. 2014</td>
<td>Herbal cannabis</td>
<td>Retrospective case study</td>
<td>Self-reported PTSD (DSM-IV) determined by telephone screening</td>
<td>2.5 years</td>
<td>80</td>
<td>4</td>
<td>Total CAPS score</td>
<td>Reduction of total CAPS scores</td>
<td>No dropouts</td>
<td>No cannabis, 98.8</td>
<td></td>
</tr>
</tbody>
</table>

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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 with PTSD and experiencing symptoms that were measured by a clinical psychometric.

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 naturalistic observational study, and one study was a retrospective chart review. Two studies were observational clinical case studies. Three studies used nabilone, a synthetic THC analog; one study used THC only; two studies used CBD oil; and four studies used smoked herbal preparations of cannabis, including resin. Results will be discussed separately per cannabinoid compound.
symptoms, which there was not. A mean reduction in the CAPS score for Recurring and Distressing Dreams was found, and secondary measures of general well-being 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 PCL-C decreased significantly, alongside greater increase in sleep and global function, reduction in nightmares. 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 cannabis use disorder (CUD), a major limitation of this study is its limited generalizability to others with PTSD and the difficulty to disentangle potential confounding 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 (2009) 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 6 mg nabilone nightly, based on efficacy and side effects, with an effective dose of 200 micrograms to 4.0 mg 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 5 mg sublingual THC twice a day, for three weeks, as an add-on treatment
Table 3. CONSORT table for pilot and feasibility trials

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1a Identification as randomized in the title</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>1b Structured summary of study design, methods, results, and conclusions</td>
<td>✓</td>
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<tr>
<td>2a Scientific background and explanation of rationale for future definitive trial and reasons for randomized pilot trial</td>
<td>✓</td>
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<td>2b Specific objectives or research questions for pilot trial</td>
<td>✓</td>
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<tr>
<td>3a Description of pilot trial design including allocation ratio</td>
<td>✓</td>
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<tr>
<td>3b Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons</td>
<td>✓</td>
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<tr>
<td>4a Eligibility criteria for participants</td>
<td>✓</td>
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<tr>
<td>4b Settings and locations where the data were collected</td>
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<tr>
<td>4c How participants were identified and consented</td>
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<tr>
<td>5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
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<tr>
<td>6a Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed</td>
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<td>6b Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons</td>
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<tr>
<td>6c If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial</td>
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<tr>
<td>7a Rationale for numbers in the pilot trial</td>
<td>✓</td>
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<tr>
<td>7b When applicable, explanation of any interim analyses and stopping guidelines</td>
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<td>8a Method used to generate the random allocation sequence</td>
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<tr>
<td>8b Type of randomization(s); details of any restriction (such as blocking and block size)</td>
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<tr>
<td>9 Mechanism used to implement the random allocation sequence (such as sequentially</td>
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<td>numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
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<td>10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
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<td>11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
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<td>11b If relevant, description of the similarity of interventions</td>
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<td>12 Methods used to address each pilot trial objective whether qualitative or quantitative</td>
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<td>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</td>
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<td>13b For each group, losses and exclusions after randomization, together with reasons</td>
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<td>14a Dates defining the periods of recruitment and follow-up</td>
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<td>14b Why the pilot trial ended or was stopped</td>
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<td>15 A table showing baseline demographic and clinical characteristics for each group</td>
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<td>16 For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomized group</td>
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<td>17 For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomized group</td>
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<td>18 Results of any other analyses performed that could be used to inform the future definitive trial</td>
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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 four weeks for eight weeks. Although the study does not report any statistical tests, it does report that the total reduction in symptoms was 28% across eight 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 to, 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 and Opila-Lehman (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 (25 mg oral capsule) daily, for six 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 100 g/month. Twenty-nine Israeli military veterans with diagnosed PTSD (using the DSM-IV-TR criteria) received treatment 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 dropout 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 with PTSD/chronic pain comorbidity (88 patients). Patients were administered “medical cannabis” (sativa species; 20%–25% THC), roughly 2 to 3 g per day. The study administered the CAPS but did not report the outcome, stating that some “positive changes in CAPS scores [were] 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 on patients evaluated for the New Mexico Medical Cannabis program. New Mexico was the first state to list PTSD as a condition for which medical cannabis could be prescribed. Eighty participants were assessed using the CAPS, which showed a significant decrease in patients using cannabis in comparison to patients who did not use cannabis. Additionally, reductions were found in CAPS subscales for reexperiencing, avoidance-numbing, and hyperarousal. 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.
used, and the screening occurred over the phone, where symptoms may have been exaggerated.

Finally, Passie, Enrich, 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 comprises small, low-quality studies, with significant limitations to the study designs, which makes 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 its 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. While 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 United States 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 are 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 CUD are greater among 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 admitted to specialized Veterans Affairs treatment programs showed poorer outcomes on severity of symptoms, violent behavior, and other drug use (Wilkinson et al., 2015). In regard 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 serious side effects (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 North America by the end of 2019, should be able to add to the evidence regarding the clinical utility of cannabinoids for PTSD while 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 more than 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, 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; more than 90% will have at least one other lifetime psychiatric disorder (Kessler et al., 1995), notably 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 preexisting 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 regard to cannabinoids for PTSD, including clinical prescription guidelines.

**Strengths and limitations**

Strengths of this systematic review include a rigorous and preregistered methodology with robust quality assessments. We used strict criteria for entry into the systematic review only including studies that 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**

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 the harms and benefits of cannabis to inform policy making and clinical decision making in regard to individual patients.

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Disclosure statement
The authors have no conflicts of interest.

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