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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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 [CB₁R] and type 2 [CB₂R]), and enzymes that catabolize the internal ligands (fatty acid amide hydrolase and [FAAH] and monoacylglycerol lipase [MAGL]). 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, & Hashimoto-Dani, 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 Δ⁷-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 (CB₁R) 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 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-HT₁₅ (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-γ) (Campos, Moreira, Gomes, Del Bel, & Guimaraes, 2012), and dopamine D₂ 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). 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 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). CB1Rs are densely expressed in the hippocampus (Chan, Hinds, Impey, & Storm, 1998). A positron emission topography (PET) 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 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 focuses on how trials were designed, analyzed, and interpreted (see Table 3). Also, an 8-item checklist (Murad, Sultan, Haflar, & 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.

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.

Nabilone

Nabilone, a synthetic THC analogue, is a CB₁R 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.
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.
Acknowledgements: We are grateful to our funders.

Disclosures: The authors have no conflicts of interest.

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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


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


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


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


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.
<p>| Nabilone | Jetly et al. 2015 | Nabilone | Pilot randomized, double-blind, placebo-controlled crossover clinical trial | PTSD (DSM-IV-TR) via CAPS | 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) |
| Cameron et al. 2014 | Nabilone | 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 ) | Increase in number of hours slept. Pre-drug: 5.0 (1.4) to post-drug: 7.2 (1.2) , ( p &lt; .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. | |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Dose</th>
<th>Duration</th>
<th>Start</th>
<th>End</th>
<th>Duration</th>
<th>Response</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraser, 2009</td>
<td>Open label Clinical Trial</td>
<td>Nabilone</td>
<td>PTSD (DSM-IV-TR) via PTSD Diagnosis Scale</td>
<td>4-12 months</td>
<td>47</td>
<td>3b</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>Started 500 micrograms, dose adjusted according to response, 1 hour prior to bedtime. Effective dose range: 200 micrograms to 4.0 mg.</td>
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<tr>
<td></td>
<td></td>
<td>Oral</td>
<td>Nightmare frequency was required to be a minimum of once weekly</td>
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</tr>
<tr>
<td>Roitman et al. 2014</td>
<td>Pilot, Open label Study</td>
<td>THC</td>
<td>PTSD (DSM-IV) via CAPS</td>
<td>3 weeks</td>
<td>10</td>
<td>3b</td>
<td>CAPS total score: Start: 94 (13.42)</td>
<td>CAPS Intrusion score: Start: 24.2 (7.75) 3w: 18.7 (7.97) p &gt;0.01, d= 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inclusion: Chronic PTSD</td>
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<td></td>
<td>Side effects reported in four cases (40%); dry mouth in</td>
</tr>
<tr>
<td>Measure</td>
<td>Start Value</td>
<td>3 Weeks Value</td>
<td>p-value</td>
<td>d-value</td>
<td>Notes</td>
<td></td>
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<tr>
<td>CAPS Avoidance</td>
<td>37.5 (6.36)</td>
<td>35.0 (6.36)</td>
<td>&lt; .01</td>
<td>0.39</td>
<td>Two patients (20%), headache in one patient (10%), and dizziness in another patient (10%).</td>
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<tr>
<td>CAPS Arousal</td>
<td>32.3 (4.73)</td>
<td>24.3 (9.11)</td>
<td>&lt; .02</td>
<td>1.10</td>
<td>No treatment discontinuations during the trial.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI - S</td>
<td>6.0 (0.47)</td>
<td>4.9 (0.99)</td>
<td>&lt; .02</td>
<td>1.42</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CGI - I</td>
<td>3.6 (0.52)</td>
<td>2.7 (1.25)</td>
<td>&lt; .03</td>
<td>0.84</td>
<td></td>
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</tr>
<tr>
<td>PSQI</td>
<td>17.2 (2.65)</td>
<td>13.9 (4.48)</td>
<td>&lt; .05</td>
<td>0.90</td>
<td></td>
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</tr>
<tr>
<td>NFQ</td>
<td>0.6 (0.3)</td>
<td>0.37 (0.33)</td>
<td>&lt; .02</td>
<td>0.41</td>
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<tr>
<td>NES</td>
<td>32.2 (11.29)</td>
<td>22.9 (8.7)</td>
<td>&lt; .002</td>
<td>0.92</td>
<td></td>
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</tbody>
</table>

Twice a day, SL

Adjusted doses depending on severity of symptoms.

diagnosed more than 1yr before entering study and at least 3 years after trauma exposure.
<table>
<thead>
<tr>
<th>Study</th>
<th>CBD/Oil</th>
<th>Dose Details</th>
<th>Methodology</th>
<th>Outcome Measures</th>
<th>Blood Pressure, Heart Rate, Weight, BMI</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elms et al. 2018</td>
<td>CBD Oil</td>
<td>Mean initial dose = 33.18 mg (SD: 23.34). Mean final dose was 48.64 mg (range 2-100) - Flexible dosing regimen</td>
<td>Retrospective Case series Open label</td>
<td>PCL-5 score &gt; 33</td>
<td>8 weeks 11 2c PCL-5 n = 8 PCL-5 score</td>
<td>No changes in blood pressure, weight, BMI or pulse</td>
</tr>
<tr>
<td>Shannon et al. 2016</td>
<td>CBD 25 mg plus 6-12 mg SL spray as needed depending on worsening of symptoms</td>
<td>Oral Capsule</td>
<td>Case report of a 10 year old girl</td>
<td>Sleep scale</td>
<td>6 months 1 3b NR NR</td>
<td>No side effects reported</td>
</tr>
</tbody>
</table>

**Cannabidiol (CBD)**

**Cannabis Preparations**
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Duration</th>
<th>Sample Size</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mashiah 2012</strong>&lt;br&gt;Herbal cannabis of roughly 23% THC and &lt;1% CBD, no greater than 100 g/month Smoked</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>CAPS</td>
<td>Total CAPS reduced baseline: 97.7 +/- 13.3 Final CAPS assessment 53.7 +/- 18.3</td>
<td>Self assessed QOL A clinician-assessment of clinical improvement</td>
</tr>
<tr>
<td><strong>Reznik, 2011</strong>&lt;br&gt;Herbal cannabis sativa species containing 20-25% THC&lt;br&gt;Daily dosage range 2-3 gr/day</td>
<td>Naturalistic observational study</td>
<td>Patients had applied to the Ministry of Health to obtain a Medical Cannabis licence. No specific measure used to determine PTSD diagnosis</td>
<td>3 years</td>
<td>167</td>
<td>CAPS</td>
<td>NR</td>
<td>QOLS CGI-I Pain scores</td>
</tr>
<tr>
<td><strong>Greer et al. 2014</strong>&lt;br&gt;Herbal cannabis Various</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>Total CAPS score</td>
<td>Reduction of total CAPS scores cannabis: 22.5 (16.9) no cannabis: 98.8 (17.6) p &lt; .0001, d = 4.42</td>
<td>CAPS re-experiencing cluster CAPS re-experiencing cluster decreased under cannabis From 29.5 (6.4) to 7.3 (5.9), p &lt; .0001, d = 3.61</td>
</tr>
</tbody>
</table>

NR: Not reported
| Passie et al. 2012 | Cannabis Resin (CBD + THC) 50:50 | 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
<table>
<thead>
<tr>
<th>Study</th>
<th>1) Random sequence generation</th>
<th>2) Allocation concealment</th>
<th>3) Blinding of participants and personnel</th>
<th>4) Blinding of outcome assessments</th>
<th>5) Incomplete outcome data</th>
<th>6) Selective reporting</th>
<th>7) Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jetly et al. 2015</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Cameron et al. 2014</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Fraser, 2009</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Elms et al. 2018</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
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<tr>
<td>Greer et al. 2014</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th></th>
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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>
<td>✓</td>
</tr>
<tr>
<td>1b Structured summary of study design, methods, results, and conclusions</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2a Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2b Specific objectives or research questions for pilot trial</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3a Description of pilot trial design including allocation ratio</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3b Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4a Eligibility criteria for participants</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4b Settings and locations where the data were collected</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4c How participants were identified and consented</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<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>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6b Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6c If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>7a Rationale for numbers in the pilot trial</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>7b When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>8a Method used to generate the random allocation sequence</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
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<td>Description</td>
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<tr>
<td>8b</td>
<td>Type of randomisation(s); details of any restriction (such as blocking and block size)</td>
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<tr>
<td>9</td>
<td>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</td>
<td></td>
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<tr>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
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<tr>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
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<tr>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
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<tr>
<td>12</td>
<td>Methods used to address each pilot trial objective whether qualitative or quantitative</td>
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</tr>
<tr>
<td>13a</td>
<td>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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<tr>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
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<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
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<td>14b</td>
<td>Why the pilot trial ended or was stopped</td>
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<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
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<td>16</td>
<td>For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group</td>
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<td>17</td>
<td>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</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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<td>19 All important harms or unintended effects in each group</td>
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<td>19a If relevant, other important unintended consequences</td>
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<td>20 Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility</td>
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<td>21 Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies</td>
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<td>22a Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence</td>
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<td>22a Implications for progression from pilot to future definitive trial, including any proposed amendments</td>
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<td>23 Registration number for pilot trial and name of trial registry</td>
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<td>24 Where pilot trial protocol can be accessed, if available</td>
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<td></td>
<td>25 Sources of funding and other support (such as supply of drugs), role of funders</td>
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<td>26 Ethical approval or approval by research review committee, confirmed with reference number</td>
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*Note. Green = present; Red = absent; Yellow = unclear; Grey = not applicable.*
Table 4. Methodological Quality Assessment for Case Reports/Case Series

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<tr>
<td>1) Clear selection method?</td>
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<td>2) Exposure adequately ascertained?</td>
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<td>3) Outcome adequately ascertained?</td>
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<td>4) Alternative causes ruled out?</td>
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<td>5) Challenge/rechallenge phenomenon?</td>
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<td>6) Dose-response effect?</td>
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<td>7) Follow up long enough?</td>
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<td>8) Sufficient reporting?</td>
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Note. Green = low potential bias; Red = high potential bias.