CANNABIS, CANNABIS-BASED PRODUCTS, OR CANNABINOIDS BRIEF EVIDENCE REPORT:

EVIDENCE FROM EXPERIMENTAL TRIALS IN PEOPLE WITH POST-TRAUMATIC STRESS DISORDER (PTSD)

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ABBREVIATIONS

AE	Adverse event
AUD	Alcohol use disorder
CAPS-(4/5)	Clinician-Administered PTSD Scale (for DSM-4 or DSM-5)
CBD	Cannabidiol
CBP	Cannabis/cannabinoid-based product
CRRB	Cannabis Research Review Board
CUD	Cannabis use disorder
CoE	Certainty of Evidence
CRRB	Utah Cannabis Research Review Board
DoD	(United States) Department of Defense
DSM-4/5-(TR)	Diagnostic and Statistical Manual of Mental Disorders–Fourth or Fifth Edition–(Text Revision)
fMRI	Functional magnetic resonance imaging
HC	Healthy controls
LOE	Level of evidence
mPFC	Medial prefrontal cortex
NASEM	National Academies of Science, Engineering, and Medicine
PCL-5	PTSD Checklist for DSM-5
PE	Prolonged exposure
PTSD	Post-traumatic stress disorder
rACC	Rostral anterior cingulate cortex
RCT	Randomized controlled trial
ROB	Risk of bias
SI	Suicidal ideation
SR	Systematic review
SRMA	Systematic review and meta-analysis
TEC	Trauma-exposed controls
THC	(delta-9)-tetrahydrocannabinol
VA	(United States) Department of Veteran's Affairs
vmPFC	Ventromedial prefrontal cortex

1.0 OBJECTIVE

Medical cannabis can be used in the treatment of post-traumatic stress disorder (PTSD) under Utah law, provided that (1) a qualified licensed provider diagnosed/confirmed the patient's PTSD, and (2) the patient is also receiving treatment/monitoring by a licensed mental health therapist.[1] The Utah Cannabis Research Review Board (CRRB) previously summarized evidence for the use of cannabis in people with PTSD; that guidance includes 1 formal (ie, graded) recommendation:

"There is insufficient evidence to support the conclusion that medical cannabis or cannabinoids are effective or ineffective treatments for PTSD or symptoms of PTSD" (page 5).[2]

Overall, current CRRB guidance for PTSD describes the results from 4 systematic reviews (SRs) of randomized controlled trials (RCTs) and observational studies published in 2017 that each reported a lack of cannabis-related RCT evidence that met their inclusion criteria. Additionally, the guidance describes how some observational evidence reported evidence of harm associated with cannabis use in people with PTSD. Thus, based on the uncertainty about the risks and benefits of cannabis use among people with PTSD, current guidance recommends considering medical cannabis for people who fail to sufficiently respond to or cannot tolerate available FDA-approved treatments or evidence-based psychotherapy, when the risks of ongoing, severe PTSD are considered to outweigh the potential risks of cannabis therapy.[2]

The **objective** of this report is to summarize experimental (ie, nonrandomized or randomized) controlled trials on the use of cannabis- or cannabinoid-based products (CBPs) in people with PTSD to assist the CRRB in determining whether updates to existing guidance is warranted.

2.0 BACKGROUND

PTSD is a serious condition resulting from exposure to a major traumatic event (eg, an event carrying a threat of serious injury or death to an individual or close family or friend) that is classified as a trauma or stress-related disorder by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR).* Patient's presenting symptoms vary but can be grouped into 4 clusters: (1) intrusive thoughts or reactions to reminders of the trauma; (2) avoidant behaviors; (3) altered mood or cognition; and (4) altered arousal or reactivity. Sleep disturbances are a possible symptom of PTSD, including as recurrent distressing dreams (an intrusive symptom) or as trouble falling/staying asleep (an alteration in arousal). To meet formal diagnostic criteria, patients must have a certain number of symptoms from each symptom cluster. Additionally, symptoms must last for more than 1 month following a traumatic exposure and cause significant distress or impairment.[3]

An estimated 6-8% of individuals will experience PTSD in their lifetime, with some individuals having a higher likelihood of developing PTSD due to environmental, genetic, cultural, or occupational factors, among others. Notably, the lifetime prevalence of PTSD in women is approximately twice that of men.[3] Psychiatric co-comorbidities are very common among people with PTSD, with over 50% of affected individuals also suffering from mood, anxiety, or substance use disorders (SUDs).[4]

The 2023 clinical practice guideline from the US Department of Veterans Affairs and Department of Defense (VA/DoD) *strongly* recommends manualized trauma-focused psychotherapy *first line* in the management of PTSD. Trauma-focused psychotherapies use "…cognitive, emotional or behavioral techniques to facilitate processing a traumatic event and in which the trauma focus is central component of the therapeutic process,"[5] and are typically delivered by a therapist proficient in the therapeutic technique over 10 to 12 weekly 60-to-90-minute sessions.[6] VA/DoD guideline-recommended trauma-focused therapies include Cognitive Processing Therapy, Prolonged Exposure (PE), and Eye Movement Desensitization and Reprocessing (each based on a moderate level of evidence [LOE]).[6] PE is among the most widely used and empirically supported trauma-focused therapies, which aims to eliminate/reduce an individual's distressing response to traumatic stimuli by repeated exposure to the stimuli (eg, with images) in a safe environment (a process known as [fear] extinction learning).[5,7]

Pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) paroxetine or sertraline, or the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine are recommended by the VA/DoD when first-line therapies are not accessible or not of interest to the patient (strong recommendation; moderate LOE).[6] The SSRIs sertraline and paroxetine are the only FDA-approved medications for PTSD treatment.[8] Prazosin, a postsynaptic alpha adrenergic receptor inhibitor,[9] is the only pharmacotherapy *weakly suggested* (low LOE) *for* the treatment of PTSD-associated nightmares by the VA/DoD guideline, whereas the guideline authors *weakly recommend against* prazosin *as monotherapy* for PTSD.[6]

Despite the existence of evidence-based therapies for PTSD, there remains a need for additional treatment options and/or improvement of existing options. Approximately half of patients remain symptomatic despite treatment with a trauma-focused psychotherapy.[10] Experts also report relatively high drop-out rates from evidence-based psychotherapy,[7,11] suggesting that interventions to improve treatment retention might help improve treatment outcomes for some patients. Guideline-recommended SSRIs tend to modestly improve PTSD symptoms, but few patients achieve remission.[12]

CBPs *are among several* investigational pharmacotherapies of interest for the treatment of PTSD based on support from pre-clinical and some observational clinical evidence.[6,12-14] Some non-experimental studies have found a relative deficiency of endogenous cannabinoids, and increased expression of available cannabinoid type 1 (CB1) receptors in brain regions associated with PTSD psychopathology in people with PTSD.[15,16] Moreover, pre-clinical evidence supports a potential role for enhancers of endocannabinoid signaling (eg, CB1 receptor agonists) in the enhancement of fear extinction and the regulation of responses to fear and/or stress.[16] Possibly through potentiation of the endocannabinoid system, preclinical studies also suggest a potential role of cannabidiol (CBD) in enhancing memory extinction and/or mitigating some PTSD symptoms.[17] Synthetic cannabinoids (eg, nabilone), cannabis or its constituents, delta-9-tetrahydrocannabinol (THC) or CBD, improved some patient's PTSD symptoms in several, but not all, descriptive and observational studies.[18]

Based on the limited available clinical and pre-clinical evidence, experts have highlighted 2 *potential paradigms* for the use of medical cannabis in the treatment/management of PTSD, including[7,16,17,19]:

1. For the ongoing/as-needed relief of symptoms, and

2. For *time-limited* use *as an adjunct* to trauma-focused psychotherapy sessions, especially exposure-based therapy (eg, to be administered on a scheduled basis in association with therapy sessions).

Experts have proposed studying CBPs, potentially including THC and/or CBD, as an adjunct to exposure-based therapy given their theoretical potential to enhance extinction learning (the therapeutic objective of exposure-based therapy).[7,16,17] Moreover, acute physiological effects of some cannabinoids (eg, anxiety reduction) might facilitate greater retention of patients in therapy.[7,17] While the therapeutic potential of adjunctive cannabinoids with therapy is yet to be confirmed in clinical trials, one expert noted a need to evaluate the optimal time to administer the CBP relative to therapy. A study in healthy volunteers suggested that adjunctive CBD would be most effective when administered directly *after* (rather than before) exposure-based therapy.[17] Notably, one group of experts (Ney et al 2023) expressed theoretical concerns about the use of cannabis to manage ongoing PTSD symptoms in an uncontrolled setting outside of therapy given the theoretical potential for cannabinoids to enhance consolidation of unpleasant memories.[19]

Some evidence also suggests potential harms from cannabis use among people with PTSD. For example, people with PTSD may be more vulnerable to developing problematic cannabis use, including cannabis use disorder (CUD). Use of cannabis by people with PTSD has also been associated with increased alcohol use and suicidal ideations and worsened depression.[20] Some observational studies have also reported associations between cannabis use an increased violent behavior, agitation, and paranoia among people with PTSD.[6,21]

PTSD is the second most common qualifying condition (after persistent pain) for medical cannabis in Utah. Among approximately 88,858 patients with an active medical cannabis card in Utah as of August 2024, 7,136 listed PTSD as a qualifying condition.[22]

3.0 RESULTS

We identified 7 placebo-controlled, double-blinded, RCTs, including 8 published records and 2 limited publication records, with the latest publication date or trial record completion date between the years 2015 and 2023. Results from the 2 trials with limited publication records have not yet been published in a journal and are only available in a non-peer-reviewed form on clinicaltrials.gov. **Notably, none of the trials included by this report are addressed by current guidance from the CRRB.**

The following sections provide an overview of characteristics of the 7 included trials (section 3.1), followed by an overview of results from each trial (sections 3.2–3.4). Refer to **Appendix A**, **Table A1** for additional details about characteristics and results of the included RCTs.

3.1 Overview of Study Design and Participant Characteristics

Included RCTs addressed the following scenarios among participants with PTSD:

1. use of multiple doses of cannabis, CBD, or nabilone for the symptomatic treatment of PTSD (N=4, including):

    Jetly et al 2015,[23] Bonn-Miller et al 2021,[24] Walsh et al 2023,[25] and NCT03248167,[26]

2. the acute effects of a single THC (as dronabinol) or CBD dose (N=2, including):
   Bolsoni et al 2022 (with 2 published records)[27,28] and NCT02069366 (with published records: Rabinak et al 2020,[29] Pacitto et al 2022,[30] and Zabik et al 2023[31]),

3. and CBD as an adjunct to massed PE (N=1, including):
   NCT05132699.[32]

Three publications that addressed the acute effects of THC (scenario 2) share the same clinical trial number and a similar approach despite reporting slightly different numbers of participants,[29-31] so we considered those publications to be the same trial.

In total, the RCTs included approximately 209 participants, of which about 130 (62%) received a CBP. All participants were adults (aged ≥ 18 years).[23,24,26,27,29-32] The proportion of male participants varied across trials. Among the 5 trials that administered multiple CBP doses, ≥ 60% of participants were male in all trials except for NCT03248167 whose population was 38.7% male.[23-26,32] In contrast, among the 2 single-dose trials, more participants were female (approximately 70-75% of total participants).[27,29-31]

Generally, most trials excluded participants with uncontrolled or severe psychiatric conditions (eg, schizophrenia, bipolar disorder, psychotic disorder, or personality disorder), and trials that administered multiple doses of CBPs tended to also exclude participants with uncontrolled or severe medical conditions.[7,23-27,30,32-35] Most trials appear to have *potentially included* participants with comorbid depression or anxiety disorders *without significant suicidality*, except for trial NCT02069366 that excluded participants with a predominant anxiety disorder or major depressive disorder in the past 6 months.[35] Except for the trials by Jetly et al 2015 and Bolsoni et al 2022 that did not report exclusion criteria regarding suicidality, included trials excluded participants with significant current suicidality and/or recent suicidal behavior.[7,23-27,30,32-35] Regarding participation by individuals with co-morbid SUDs and/or evidence of illicit substance use, most trials excluded people with positive drug screens for non-prescription drug use, which sometimes included cannabis/THC (as with Jetly et al 2015 and NCT015132699),[23,24,32,34] and/or people meeting diagnostic criteria for most SUDs.[26,27,32-35] Participants with *mild* cannabis use disorder (CUD) were eligible to participate in the trial by Bonn-Miller et al 2021.[24] Some trials did not specifically exclude participants with alcohol use disorder (AUD) at baseline (Jetly 2015, trial NCT05132699)[23,32] and the trial NCT03248167 *only* enrolled participants with moderate to severe AUD with a desire to stop or reduce alcohol use.[26]

Except for the trial by Jetly et al 2015 that used *DSM-4* criteria for PTSD diagnoses,[23] included trials used the *DSM-5* criteria.[7,24-27,30,34] Among the 5 trials that administered multiple CBP doses (scenario 1 or 3), most participants probably had at least moderate severity PTSD symptoms based on reported mean baseline clinician- or patient-reported total symptom scores or the minimum symptom score required for participation.[23,24,26,32,35] Of the 7 trials, 3 multi-dose CBP trials required participants to have chronic PTSD (with diagnosis/symptoms present for ≥ 6 months or ≥ 2 years before the trial),[23-25] whereas the remaining trials did not require participants to have a minimum duration of PTSD and did not describe trial participant's PTSD chronicity.[7,26,27,29-31,34,35] Two trials (Bonn-Miller et al 2021 and Walsh et al 2023) required participants to have failed at least 1 evidence-based treatment for PTSD.[33,34] Most trials allowed participants to continue stable doses of non-interacting medications and/or psychotherapy

during the trial,[7,23-25,32] except for trial NCT03248167 that disallowed serotonergic-acting medications and recently started psychotherapy,[26] and trial NCT02069366 that disallowed recent use of SSRIs and ongoing exposure-based psychotherapy.[35] The single CBP dose trial by Bolsoni et al reported that about 50% of participants had been taking a psychiatric medication (of unknown type), but did not report information about concurrent psychotherapy.[27]

The studied CBP, dose, route of administration, and treatment duration varied between all included trials. Of the 2 trials that administered a single dose and measured acute effects either on the same day or up to 1 week later, 1 trial administered oral dronabinol (ie, synthetic THC) 7.5 mg[35] and the other administered oral CBD 600 mg (99.6% purity dissolved in corn oil and packaged in a gelatin capsule).[27] The trial that studied CBD as an adjunct to PE administered oral CBD (Epidiolex) 250 mg twice daily (before high fat meals in morning and evening), starting 3 days before PE and continued for a total of 18 days.[7,32] Remaining trials that evaluated multiple CBP doses for symptomatic treatment evaluated 3 different cannabis strains (up to 1.8 grams/day) administered by smoking using a metal pipe for 3 weeks,[24] 2 strains of cannabis (up to 2 grams/day) administered by vaporization for 3 weeks,[25] oral nabilone 0.5-3 mg nightly for 7 weeks,[23] or oral CBD 600 mg daily for 6 weeks.[26] Other than describing use of a portable vaporizer by the trial that administered vaporized cannabis, trials that administered smoked or vaporized cannabis did not describe (in their publications) exactly how it was administered; each trial used strains containing different THC and CBD concentrations (see **Appendix A** for details), but did not specify concentrations of other herbal cannabis constituents.[24,25]

3.2 Trials of Multiple Doses of CBPs for Symptomatic Treatment

We included 4 double-blinded RCTs that evaluated the use of multiple doses of CBP(s) for symptomatic treatment of PTSD; of these, one trial (NCT03248167) has only limited results posted to clinicaltrials.gov,[26] and another published only exploratory uncontrolled results (with-in participant differences from baseline) due to only reaching 14% of the targeted total enrollment (Walsh et al 2023).[25] Thus, we primarily focus on results from the trials by Jetly et al 2015 and Bonn-Miller et al 2021.

Bonn-Miller et al 2021 performed a parallel group and placebo-controlled trial (during phase I) that evaluated 3 different patient-titrated smoked cannabis options (high THC, balanced THC/CBD, high CBD) or placebo cannabis among 80 adult US military veterans (90% male) with chronic PTSD (per DSM-5 criteria) of moderate severity* at baseline (mean PCL-5 score[36] of about 44†).[24,33] The trial also included a second non-placebo-controlled phase in which a subset of participants were re-randomized to a different cannabis option; refer to **Appendix A** for results from that phase. Concurrent use of medications and/or psychotherapy was allowed if the use was considered 'stable' at baseline; the

* While not addressed in the publication by Bonn-Miler et al, the study's protocol posted to clinicaltrials.gov described that patients were required to be treatment-resistant, having failed or not tolerated an FDA-approved drug and/or evidence-based psychotherapy for PTSD.

† The PCL-5 measures patient-reported PTSD symptoms per the DSM-5. Total severity score ranges between 1 and 80; scores at or above approximately 31 are typically indicative of PTSD. While a clinically significant change on the PCL-5 has not been established according to the VA, changes of 5+ points have been considered reliable and 10+ point changes were considered clinically significant on the PCL that used *DSM-4* PTSD symptoms.

authors did not describe usage of these therapies in the trial population.[24] Major uncontrolled medical considerations, serious psychiatric comorbidities, moderate or severe CUD, and evidence of use of non-prescribed opioids, amphetamines, or cocaine or a SUD diagnosis other than CUD (per the trial protocol) were exclusionary.[33] Notably, while participants agreed to abstain from cannabis use for at least 2 weeks before starting and during the trial, investigators estimated that between 25-40% of the trial population likely continued cannabis use close to trial commencement; all treatment groups exhibited moderate mean cannabis withdrawal symptom scores at baseline, with some participants exhibiting symptoms that persisted during trial phase I.[24]

Overall, as desired smoked use high THC, balanced THC/CBD, or high CBD cannabis did not significantly reduced mean CAPS-5[37‡] scores (primary outcome) or patient-reported past-week PCL-5 scores from baseline to 3 weeks compared to placebo. Compared to baseline, total CAPS-5 scores were reduced from baseline at 3 weeks in each treatment group, including the placebo group. Cannabis use also failed to significantly improve other secondary efficacy outcomes (eg, insomnia, psychosocial functioning, society anxiety symptoms) from baseline to 3 weeks compared to placebo. Overall, most adverse events (AEs) during cannabis use were of mild to moderate severity; the most common AEs overall (each with incidence >10%) were cough, throat irritation, and anxiety. During phase I, 1 out of 20 (5%) participants in the high CBD cannabis arm experienced treatment-related suicidal ideation (SI); and during phase 2, 1 participant in each cannabis group (up to 5.5%) also reported SI. One patient (5%) withdrew from high THC cannabis due to an unspecified AE (none withdrew from another treatment group); and 4 (5.4% of all 3 cannabis groups) additional patients (2 each in the high THC and high CBD cannabis groups) withdrew during phase 2.[24]

Bonn-Miller et al pointed to several limitations that could have affected their results. Firstly, possible differences in cannabis withdrawal symptoms between study groups (particularly in the placebo group relative to cannabis groups) could have confounded the efficacy results. Secondly, the placebo group exhibited a higher-than-expected response, reducing the ability of the study to detect a difference in the primary outcome. Thirdly, participants used lower than expected daily doses of cannabis (mean of 8.2 to 14.6 grams consumed over 3 weeks when they had access to up to 37.8 grams), and possibly, the study was too short to detect differences from placebo.[24]

Walsh et al 2023 designed a similar trial to Bonn-Miller et al, except for using only 2 types of cannabis, high THC or balanced THC/CBD, and by delivering cannabis via vaporization instead of smoking. The limited number of participants (n=6) were primarily male (83.3%) with chronic, treatment-resistant PTSD of moderate severity at baseline. Cannabis treatment was associated with a modest numerical reduction in PTSD severity (per total CAPS-5 scores) from baseline to 3 weeks that was not statistically significant.[25] The small sample size and lack of comparator group precludes firm conclusions. No safety results were reported.[25,34]

‡ CAPS is a 30-item clinician-administered scale for PTSD assessment, which is based on the *DSM-IV* PTSD criteria (CAPS-4) or *DSM-V* PTSD criteria (CAPS-5). The CAPS-5 is the gold-standard measure for PTSD diagnosis according to the VA. It involves a professional asking structured questions about a specific index trauma, which can be assessed based on past week, past month, or worse ever (lifetime) symptoms. Total CAPS-5 scores range between 0 and 80, with higher scores indicating worse PTSD symptoms.

A parallel group, placebo-controlled, double-blinded RCT **(NCT03248167)** evaluated the use of oral CBD 600 mg daily for 6 weeks compared to placebo for the treatment moderate-to-severe alcohol use disorder (primary objective) among 30 participants with comorbid PTSD or subthreshold PTSD without other serious medical or psychiatric conditions. Notably, mean PCL-5 scores in both the CBD and placebo arms at baseline were above the minimum score suggestive of PTSD (mean 42 [CBD arm] or 49 [placebo arm]); however, the standard deviation (about 13.8) suggests some patients may not have met criteria for PTSD. Both CBD and placebo *numerically* reduced the mean number of drinks per day (primary outcome) and total PCL-5 PTSD score from baseline to week 6. The authors did not report a statistical analysis, but differences in the mean PCL-5 total scores at baseline and week 6 appeared to be non-significant using a simple t-test[§].

No serious AEs were reported. AEs among the CBD arm with an incidence ≥10% and ≥5% greater than the placebo arm include diarrhea, headache, and nausea. Participants in the CBD group experienced a numerically increased incidence of feeling overwhelmed, lack of motivation, and SI, whereas a numerically higher incidence of anxiety and nightmares were reported by the placebo group. Notably, only 70% of participants who started the trial completed it.[26] Overall, the high trial withdrawal rate, small sample size, and lack of published statistical analysis preclude forming firm efficacy conclusions.

Jetly et al 2015 investigated the use of oral nabilone 0.5 to 3 mg (mean dose 1.9 mg) before bedtime for the treatment of sleep disturbances in a *cross-over*, placebo-controlled, double-blind RCT among approximately 10 male activity duty military personnel with chronic PTSD per DSM-IV-TR criteria. Trial participants had CAPS (inferred as CAPS-4) distressing dream and difficulty falling/staying asleep sub-item scores exceeding 5 at baseline and lacked serious medical conditions. Stable use of medications and/or psychotherapy was allowed during the trial.[23]

Compared to placebo, nabilone significantly reduced mean CAPS recurring/distressing dream scores, but not difficulty falling/staying asleep item scores, from baseline to 7 weeks. At the end of the 7-week treatment period, 44% versus 0% of participants reported no distressing dreams in the past week during the nabilone versus placebo treatment periods, respectively. Nabilone treatment also significantly improved changes in patient-reported well-being from baseline to 7 weeks compared to placebo. Overall, investigators considered nabilone to be well-tolerated. The most common AEs associated with nabilone treatment were dry mouth and headache. Given the small sample size, investigators suggested that additional confirmatory trials are needed.[23]

3.3 Trials of a Single CBP Dose

Two parallel group, placebo-controlled, double-blinded RCTs evaluated the impact of administering a single dose of a CBP prior to laboratory-based behavioral tests on patient-reported acute symptoms and/or functional brain changes per functional magnetic resonance imaging (fMRI).[27,35] We included five

[§] Based on two separate 2-sample t-tests with equal variance (for between-group differences in mean scores at baseline and the other for differences at week 6). We were unable to perform a simple test for the between-group difference in the mean score change from baseline because the authors did not report the standard deviation for the change in mean scores.

publications from the 2 RCTs. Three publications share the same registered trial number (NCT02069366; Rabinak et al 2020, Pacitto et al 2022, and Zabik et al 2023), so we believe that there was overlap in the participants reported in each publication despite slight differences in the reported participant numbers.[29-31]

Bolsoni et al 2022 included 33 adults (75.8% female) from Brazil with PTSD (baseline PCL-5 score 53) with sexual (42.4%) or non-sexual trauma (57.6%) and without substance use or psychiatric comorbidities other than depression or anxiety. In the overall study population, a single dose of CBD 300 mg administered 90 minutes before behavioral tests significantly attenuated the effects of traumatic memory recall on patient-reported cognitive impairment (eg, confusion, difficulty reasoning), but not anxiety, sedation, or discomfort, compared to placebo. The same pattern was observed 1 week later when participants recalled their traumatic memory but did not receive another dose of CBD or placebo, suggesting the impact of CBD on cognitive impairment might persist for at least 1 week.[27] Notably, in a post-hoc analysis comparing trauma type subgroups (sexual vs non-sexual trauma), CBD significantly attenuated anxiety and cognitive impairment after trauma recall compared to placebo in the non-sexual trauma subgroup only.[28]

The **NCT02069366 RCT** included up to 71 right-handed US adults who met DSM-5 criteria for PTSD (n=19 to 22 in the PTSD subgroup depending on the publication/sub-study) from a civilian trauma, reported exposure to a civilian trauma but did not meet criteria for PTSD (trauma-exposed control subgroup [TEC]) or lacked any trauma exposure or PTSD (healthy control subgroup [HC]).[29-31,35] Patient characteristics varied slightly between sub-studies, but generally, most participants in the PTSD subgroup were female (range 68–74% across sub-studies) with a mean baseline CAPS-5 score of approximately 34.[29-31] Participants with PTSD were without major psychiatric (including a primary anxiety disorder), or substance use comorbidities and were not actively receiving SSRIs or exposure-based PTSD therapy during the trial.[35] According to 2 sub-trials (Rabinak 2020, Pacitto 2022), approximately 30% of the PTSD population reported cannabis use in the 30 days preceding the trial.[29,30] Participants in each subgroup (PTSD, TEC, and/or HC) were randomized to a dronabinol or placebo, which were administered 120 minutes before an fMRI.[29-31]

Overall, the sub-trials of NCT02069366 found that a single dose of THC (as dronabinol) significantly impacts activation of certain corticolimbic brain regions during a Threat Processing Task and extinction learning protocol, and emotional processing brain regions during an Emotional Regulation Task.[29-31] Each publication from NCT02069366 reported many comparisons between study populations (ie, those with PTSD vs TEC and/or HC), drug groups (THC vs placebo), and timing of response, among others (see **Appendix A Table A1**), which were statistically adjusted for multiple comparisons. The following is a summary of *select results* from each sub-trial, focused on comparisons between THC and PBO, primarily among participants with PTSD:

- Among participants with PTSD who completed a validated threat processing task during an fMRI, receipt of a single 7.5 mg dose of oral THC significantly acutely reduced activation of the amygdala and increased medial prefrontal cortex/rostral anterior singular cortex (mPFC/rACC) activation compared to placebo. THC also acutely enhanced functional connectivity between the mPFC/rACC and right superficial division of the amygdala, including by significantly decreasing connectivity

during the threat versus non-threat condition. Overall, authors suggested that their results support a role of THC in modulating the processing of threats by the corticolimbic system among people with PTSD.[29]

- During an Emotional Regulation Task, a single 7.5 mg dose of THC significantly increased acute cerebellar activation when viewing neutral images compared to placebo among people with PTSD. Additionally, THC normalized angular gyrus activation in people with PTSD to a degree comparable to the higher activation at baseline among TEC, and attenuated cerebellum activation while viewing neutral images or cognitively reappraising negative images in people with PTSD. Generally, participants (including those with PTSD and TEC) who received THC had a lower self-reported negative affect when reviewing unpleasant images compared to placebo; moreover, ratings for the degree of negative affect were significantly negatively correlated with activation of the posterior cingulate cortex/precuneus among THC recipients. Authors suggested that their results support investigating THC as an adjunctive therapy among people with PTSD undergoing cognitive reappraisal therapy.[30]
- Using a fear extinction experimental protocol that involved conditioning participants to a 'fear' stimulus (day 1), followed by extinction learning that unpairs the learned stimuli (day 2) and recall of the extinction and relearning of the fear (day 3), Zabik et al observed some differences in the activation of brain regions considered important to extinction learning retainment between people with and without PTSD and in people with PTSD who received THC. Compared to placebo, people with PTSD who received a single dose of THC 7.5 mg (administered before fMRI on day 2) exhibited greater left amygdala activation during early fear renewal on day 3. Additionally, compared to TEC who received THC, people with PTSD exhibited significantly increased early ventromedial prefrontal cortex (vmPFC) activation (versus late) during extinction learning. A recognized limitation of PE, one of the first-line psychotherapies for treatment of PTSD that uses extinction learning, is loss of response among initial responders; thus, based on the preliminary observations of this trial, Zabik et al proposed that future studies could explore THC as an adjunct to fear extinction psychotherapies.[31]

3.4 Trial of CBPs as an Adjunct to Psychotherapy

Limited results from a small, parallel group, placebo-controlled, double-blind *pilot* RCT (**NCT05132699**) of CBD as an adjunct to "massed" (ie, compressed duration) PE for treatment of PTSD have been posted to clinicaltrials.gov[32]; additionally, trial investigators published the study's protocol.[7] As a pilot trial, the primary objectives of the trial were to examine feasibility, along with preliminary efficacy, safety, and biological plausibility (eg, associations between levels of endogenous endocannabinoids and post-treatment PTSD severity).[7] Notably, complete results, including statistical analyses for posted results are lacking and have not been peer reviewed, and thus, should be considered preliminary.

US adults (n=21; 62% male) with PTSD (per CAPS-5 criteria; mean total scores of about 42) on a stable medication regimen and without serious medical or psychiatric comorbidities were randomized to CBD (as Epidiolex) 250 mg twice daily for 18 days or placebo in combination with PE, with stratification by PTSD severity and population (military or other).[7,32] While current use of opioids, cocaine, methamphetamines or cannabis as evidenced by a urine screening test were exclusionary, as was a primary severe alcohol use disorder, the trial may have included patients with less severe alcohol use

disorder. PE was delivered by trained study therapists and included ten 90-minute sessions given daily on weekdays over 14 days; CBD or placebo was administered for 3 days prior to PE commencement.[7]

Mean CAPS-5 and PCL-5 scores were numerically reduced from baseline to day 45 (about 1-month after the last PE session) in both the CBD and placebo groups. While numerical reductions in total scores tend to favor the placebo group when using the CAPS-5 scale, they tend to favor CBD when using the PCL-5 scale. The authors did not report a statistical analysis, but differences in the mean PCL-5 and mean CAPS-5 total scores at baseline and at 1-month follow-up appeared to be non-significant using a simple t-test[**]. No serious AEs were reported. The incidence of GI issues (CBD, 36.4%; PBO, 20%), emotional problems (CBD, 27.3%; PBO, 10%), and sleep disturbances including increased nightmares and insomnia (CBD, 36.4%; PBO, 0%) were numerically higher in group that received CBD compared to placebo.[32] *Not all planned outcomes per the study protocol have been posted to clinicaltrials.gov.*

4.0 RISK OF BIAS AND SELECT LIMITATIONS

SRs identified by our literature search only addressed the risk of bias (ROB) for 3 of 7 included trials (Jetly et al 2015, Rabinak et al 2020, and Bonn Miller et al 2021). Overall[††], reviewed SRs considered the trial by Bonn-Miller et al to carry a *low ROB,* whereas the trials by Jetly et al and Rabinak et al were rated as having a *high ROB* and *unclear ROB (ie, some concerns),* respectively[‡‡].[21,38] A high ROB rating was assigned to the trial by Jetly et al 2015 due to insufficient reporting of details about randomization, allocation concealment, and baseline characteristics, as well as concerns arising from insufficient reporting (no reporting of outcome details from each treatment period) and using an inappropriate statistical analysis for the cross-over design.[21]

Of the 4 trials without a ROB rating by an SR, two have yet to be published in a peer-reviewed journal, limiting assessment of bias. Although we did not perform a comprehensive ROB analysis, we noted that the 2 other trials (Walsh et al 2023 and Bolsoni et al 2022) may at least be at risk for bias from randomization and/or allocation concealment. Walsh et al did not report sufficient details to assess the sufficiency of randomization or concealment methods.[25] Bolsoni et al reported insufficient details to assess the adequacy of allocation concealment.[27]

Confounding bias could have distorted some trial's efficacy results. Most notably, cannabis withdrawal symptoms could have affected overall PTSD and insomnia symptoms in the trial by Bonn-Miller et al

[**] Based on two separate 2-sample t-tests with equal variance (for between-group differences in mean scores at baseline and the other for differences follow up). We were unable to perform a simple test for the between-group difference in the mean score changes from baseline because the authors did not report the standard deviation for the change in mean scores.

[††] When there was disagreement in the ROB ratings between reviewed SRs, the listed overall bias rating is the highest risk rating of the sources.

[‡‡] Bias ratings are based on the Scottish Intercollegiate Guidelines Network (SIGN) system that includes possible overall bias ratings of low, moderate or high (per Ayers et al, for Bonn-Miller et al 2021 and Jetly et al 2015), and Cochrane ROB tool that assigns ratings of low, unclear, or high ROB (per Bilbao et al 2022, for Rabinak et al 2020). Rabinak et al was assigned an overall rating of 'unclear' due to having 'unclear' ratings for the individual bias domains of random sequence generation and allocation concealment (and 'low' rating on other domains).

2021 (see section 3.2 for details).[24] Significantly more participants in the CBD treatment group had a mood and/or anxiety disorder at baseline compared to the placebo group (88.2% vs 37.5%) in the trial by Bolsoni et al 2022, which potentially could have distorted behavioral or psychological outcome scores.[24] We also noted that nearly all trials allowed participants to continue stable medication and/or psychotherapy regimens (ie, including those used to treat PTSD), but trials except for Bolsoni et al and NCT02069366 did not describe the utilization at baseline and no trial described possible changes in utilization during the trial.[7,23-26,29,32] If utilization of these therapies differed between treatment groups during the trials, it could have affected the outcome results.

Generalizability of findings to patients with PTSD in Utah who seek medical cannabis treatment is a potential concern:

- Unlike other included trials, Jetly et al 2015 used *DSM-4-TR* criteria to confirm participant's PTSD diagnoses.[23] Because there are significant differences in diagnostic criteria between the *DSM-4-TR* and *DSM-5* criteria (only approximately 55% overlap according to 1 study),[4] it is possible that characteristics of participants included by Jetly et al 2015 could differ from patients meeting *DSM-5* criteria for PTSD. Yet, Jetly et al targeted sleep disturbances among participants with PTSD, which remains as part of possible criterion for PTSD per the *DSM-5*.[3,4] Its also unknown whether nabilone's benefits for sleep disturbances observed by Jetly et al would be similarly observed with cannabis products used by Utah medical cannabis patients.
- *Generally*, most of the trials excluded major psychiatric comorbidities and trials that administered multiple CBP doses also tended to exclude patients with serious medical comorbidities,[7,23-27,30,32-35] limiting assessment of efficacy and safety in such populations. The largest and arguably most robust included RCT by Bonn-Miller et al likely had somewhat selective eligibility criteria considering that 127 of 261 (48.7%) screened patients did not meet the trial's inclusion criteria (that could have been due to co-morbidities or not wanting to abstain from cannabis use for 2 weeks, among other reasons), and an additional 54 (20.7%) declined participation or were loss to follow-up.[24]
- It is unknown/unclear whether response to CBPs depends on characteristics such as PTSD severity, type of trauma, PTSD duration, and/or PTSD subtype. While 3 of 5 included trials that administered multiple CBP doses targeted patients with chronic PTSD (eg, symptom duration ≥ 6 months),[23-25] generally, little information was provided about clinical characteristics of included patients. We infer that most participants in the 5 trials that administered multiple CBP doses likely had at least moderate severity PTSD based on reported mean baseline clinician- or patient-reported total symptom scores or the minimum symptom score required for participation.[23,24,26,32,35] Notably, participants in the only trial with a reported statistically significant benefit from a CBP over placebo (Jetly et al 2015) were all men with chronic PTSD (since ≥ 2 years prior) with sleep disturbances at baseline whose index traumatic event occurred during military service.[23]

5.0 CONCLUSIONS FROM RECENT SYSTEMATIC REVIEWS AND/OR GUIDELINES OR TREATMENT ALGORITHMS

Two recent SRs (Rodas et al 2024, and Ayers et al 2021, with an updated literature search in 2024) evaluated evidence from controlled clinical trials and high-quality controlled observational studies

(Ayers et al) and/or any observational studies or case-series (Rodas et al) on the management of PTSD with cannabis or cannabis-based products. Both SRs included the RCTs by Bonn-Miller et al 2021 and Jetly et al 2015, in addition to 5 cohort studies (Ayers et al) or 12 observational or descriptive studies (Rodas et al).[18,21] The following are key conclusions from these reviews:

- Rodas et al 2024[18]:
  - Rodas et al assessed the potential effectiveness of cannabis/cannabinoids for PTSD by DSM-5-specified PTSD symptom clusters. Based primarily from evidence considered to have a moderate to high ROB, they suggested that cannabinoids are *possibly* beneficial for sleep disturbances (cluster B and E symptoms), rather than for overall PTSD symptom improvement.[18]
  - Regarding safety, some studies included by Rodas et al reported worsening SI and violent behavior associated with cannabis use. Moreover, Rodas et al found that all studies among people with PTSD and CUD (N=3 observational and/or descriptive studies) tended to report an association between cannabis use and worsening of overall PTSD symptoms.
- Ayers et al 2021 (updated 2024):
  - "There is low CoE [certainty of evidence] that cannabis does not affect PTSD symptoms, general depression, or social anxiety"[39]
  - There is "…very low CoE for improvement in the intensity and frequency of disturbing dreams with nabilone" (page 14).[21]
  - No differences in global or psychosocial functioning were found with cannabis use (very low CoE). Ayers et al noted that no evidence addressed the impact of cannabis on quality of life.[21,39]
  - Regarding safety, cohort studies found that cannabis use in people with PTSD was associated with higher substance abuse scores compared to scores among people with PTSD who discontinued or never used cannabis. In one cohort study, cannabis "…starts had significantly more violent behavior than continuing users, never-users, and stoppers at follow-up (P<.0001)" (page 13).[21]

The 2023 VA/DoD PTSD guideline strongly recommends against the treatment of PTSD with cannabis or cannabinoid-related compounds due to a lack of high-quality efficacy evidence along with some evidence suggesting the potential for serious harms (eg, impaired attention/memory, increased substance use, psychiatric AEs including suicide attempts or paranoia, among others). To form this recommendation, the VA/DoD guideline workgroup performed a comprehensive literature search for SR or RCT evidence of cannabinoid interventions (versus comparator) in adults with PTSD and rated the quality of evidence for their recommendation against cannabis use as very low.[6] Similarly, a 2022 expert opinion PTSD treatment algorithm for medication use suggests against cannabis as part of routine care given the limited efficacy evidence and the potential for harm (eg, increased irritability and/or poor anger management); *yet, authors also included cannabis-related products among last-line pharmacotherapeutic options for treatment-resistant symptoms*.[13] Another expert opinion guidance focused on the treatment of chronic pain with cannabis (Bell et al 2023) recommended cannabis-based medicines for people with chronic pain and PTSD who had an insufficient response or who cannot tolerate non-pharmacologic treatments based on low-quality evidence (all cited evidence was non-experimental).[40]

6.0 SUMMARY

We identified 7 (10 records) double-blinded, placebo-controlled RCTs that evaluated use of CBPs among approximately 209 adults with PTSD in total that were not addressed by previous CRRB guidance for the management of PTSD with medical cannabis. The RCTs evaluated CBPs using 3 treatment paradigms, including: (1) as a symptomatic treatment for PTSD over 3 to 7 weeks (N=4; with smoked or vaporized cannabis, nabilone, or CBD)[23-26]; (2) as a single dose (of CBD or dronabinol) to assess *acute* symptoms or behavioral effects (N=2)[27,35] in a laboratory setting; and (3) as an adjunct to PE (N=1; with CBD) for treatment of PTSD.[32] Notably, only limited conclusions can be drawn from 3 of the 7 RCTs because 2 have only been published on clinicaltrials.gov and have only descriptive results available,[26,32] and the third analyzed the results without a control group due to under recruitment of participants.[25]

Overall, while the 2 RCTs that examined a single dose of THC or CBD suggest that CBPs acutely affect brain regions implicated in PTSD or cognition among people with PTSD,[27,29-31] 3 longer trials that evaluated the ongoing use of CBPs for up to 6 weeks tend to suggest that cannabis may not be better than placebo for most PTSD symptoms.[24-26] One small 7-week cross-over trial (Jetly et al 2015) among active military men with PTSD (per *DSM-IV-TR* criteria) characterized by sleep disturbances, found that nabilone 0.5 to 3 mg nightly significantly reduced recurring/distressing dreams but not patient-reported difficulty falling or staying asleep from baseline compared to matched placebo.[23] Participants in the Jetly et al trial reported a continuation of regular dreams during nabilone treatment.[23]

While sleep disturbances are a core feature of PTSD, no trial other than Jetly et al 2015 targeted only people with PTSD-associated sleep disturbances. Nor did included trials evaluate the same sleep disturbance outcomes as Jetly et al 2015, although some sleep-related results were reported by other trials. Like the results for overall PTSD symptoms, Bonn-Miller et al found that *ad libitum* smoked cannabis (as a chemovar with high THC, balanced THC/CBD, or high CBD) significantly improved patient-reported insomnia symptoms on the Insomnia Severity index from baseline to 3 weeks; however, a similarly robust response was achieved among placebo cannabis recipients.[24] Notably, participants in each treatment group of the Bonn-Miller et al trial had moderate mean levels of cannabis withdrawal, which possibly confounded the efficacy results.[24] In 2 other trials, sleep disturbances (nightmares and/or insomnia) were reported as AEs with different directions of effect: oral CBD 250 mg twice daily as an adjunct to PE for 14 days was associated with numerically increased nightmares and insomnia versus placebo (36% versus 0%, respectively),[32] whereas numerically more placebo recipients (15.4%) reported nightmares compared to CBD 600 mg daily recipients (5.9%).[26] Such observations are only descriptive, however, and could be from random variation or attributable to other differences in the trial populations or design.

Because a single dose of oral dronabinol 7.5 mg favorably attenuated or activated some brain regions implicated in threat and emotional processing among people with PTSD during laboratory-directed threat processing, emotional regulation, and fear-extinction protocols, laboratory trial investigators suggested that THC could be investigated as an adjunctive treatment during cognitive reappraisal and/or fear extinction-based psychotherapies (eg, PE).[29-31] A single oral dose of CBD 300 mg administered 90 minutes before behavioral tests in people with PTSD attenuated the effects of traumatic recall on

patient-reported cognitive impairment[27]; patient reported anxiety was also improved with CBD versus placebo in the subgroup with non-sexual trauma only (per a *post-hoc* analysis).[28] Preliminary descriptive results from the only included trial that investigated CBD (as Epidiolex) 250 mg twice daily as an adjunct to massed PE started 3 days before 10 daily PE sessions over 14 days suggests that adjunctive CBD and placebo may be similarly effective at 1 month after PE completion.[32] However, the results for all planned trial outcomes,[32] and statistical analyses from this trial have not yet been published, precluding firm conclusions.

Generally, among trials that reported information about AEs (N=5), the studied CBPs were associated with primarily mild to moderate severity AEs.[23,24,26,32,35] On average, based on changes in total PTSD symptom scores among trials reporting that outcome, treatment with smoked or vaporized cannabis, or CBD was not associated with worsened PTSD symptoms in the short-term.[24-26,32] Yet, some psychiatric AEs occurred at a numerically higher incidence compared to placebo. Approximately 4 participants (3.6%–5.9% per treatment group) who received smoked cannabis for up to 3 or 6 weeks (depending on completion of both 3-week trial phases) endorsed SI.[24] In another trial, one participant (5.9%) with comorbid moderate-to-severe AUD who received oral CBD 600 mg endorsed SI compared to none in the placebo group.[26] Other psychiatric AEs, each classified as non-severe, reported numerically more frequently by the CBP group in least 1 trial include anxiety (studied CBP: smoked cannabis),[24] feeling overwhelmed (oral CBD),[26] lack of motivation (oral CBD),[26] and emotional problems (oral CBD).[32]

When evaluating the safety of CBPs based on included trials, it should be considered that most trials excluded patients particularly vulnerable to psychiatric AEs. For example, most trials excluded participants with serious suicidality, substance use disorders (with some exceptions for CUD and/or AUD), and psychotic disorders at baseline.[7,23-27,30,32-35] Moreover, the included trials were of a relatively short duration, precluding conclusions about the long-term safety or efficacy of CBPs for people with PTSD.

Overall, heterogeneity in the studied CBP, treatment duration, and studied population characteristics, along with limitations of the available evidence, including the small sample sizes, potential bias and confounding, and incomplete reporting of results (from trials only published on clinicaltrials.gov) prevent forming firm conclusions about the efficacy of cannabinoids or cannabis-based therapy for people with PTSD.

7.0 CONSIDERATIONS FOR THE CRRB PTSD GUIDANCE DOCUMENT

If desired, the CRRB may consider updating guidance on the treatment of PTSD with medical cannabis based on this review. Historically, the CRRB has assigned level of evidence (LOE) ratings (eg, “limited” or “insufficient”) from the National Academies of Sciences, Engineering, and Medicines (NASEM) to formal recommendations in guidance documents. Refer to **Appendix B** for a summary of LOE categories and corresponding criteria from NASEM.

7.1 Considerations for Formal (ie, Graded) Recommendations

- May consider maintaining the current statement: "There is insufficient evidence that medical cannabis or cannabinoids are effective or ineffective treatments for PTSD or symptoms of PTSD."
    - Although we included 7 RCTs, the trial's designs, nature of reported results, and/or potential bias or limitations preclude forming firm conclusions about the efficacy of cannabis for management of PTSD symptoms.
    - Of the 4 included RCTs that evaluated cannabis or cannabinoids for 3 to 7 weeks as a symptomatic treatment for PTSD, one trial lacked a comparator group due its small size[25] and only descriptive results from clinicaltrials.gov are available for another, although our simple statistical analysis suggests that mean PTSD total symptom scores did not significantly differ between the CBD- and placebo-treated groups.[26] One of the remaining 2 trials considered to have a high ROB[21] found nabilone for 7 weeks significantly reduced recurring/distressing dreams from baseline compared to placebo among military personnel selected for having sleep disturbances.[23] Whereas, in the other trial of military veterans considered to have a low risk of bias,[21] smoked cannabis for 3 weeks improved overall PTSD symptoms and patient-reported insomnia to a similar degree as placebo.[24]
    - While updates to the formal graded statement may not be necessary, the CRRB should consider adding descriptive information about major results from key trials to guidance (see **section 7.2**).
- May consider adding a new statement about the use of cannabis or cannabinoids as an adjunct to psychotherapy for PTSD:
    - There is interest in using cannabis or cannabinoids as an adjunctive therapy to psychotherapy (ie, administered on a time-limited basis in association with therapy), but only 1 included trial addressed this treatment paradigm and complete results from that trial have not yet been published. Numerical findings and our simple statistical tests for differences in mean total PTSD symptom scores at baseline and follow-up suggest that adjunctive CBD and placebo were similarly effective.[32] Overall, evidence could be considered insufficient.
    - Notably, it is possible that participants in other trials were receiving some form of psychotherapy during the trial, as trials that administered multiple CBP doses allowed the participation of people receiving 'stable' therapy (ie, excluding new/recent initiators of therapy). Trials that allowed for concurrent 'stable' therapy did not describe how many and which participants in each study arm received therapy, nor did they report outcomes specifically among therapy recipients.[23-26]
    - The CRRB may consider following up on complete results from NCT05132699 (that investigated CBD as an adjunct to massed PE) once published. At the time of writing this report, only limited results for select outcomes and without statistical analyses had been posted to clincialtrials.gov.[32] We are also aware of an ongoing trial of CBD as an adjunct to PE in the treatment of PTSD (NCT03518801) that is estimated to have been completed on September 30, 2024; at the time of writing this report, results had not yet been posted to clinicaltrials.gov.[41]

7.2 Additional Considerations

- Particularly for included RCTs that have been published in a peer-reviewed journal, consider including information about characteristics, such as the study design, major clinical characteristics of included participants, the types and routes of administration of cannabis or cannabinoids used, and major bias or limitation concerns. Refer to **section 3.1** (trial characteristics) and **section 4.0** (bias and limitations) for details.
- Consider discussing/reviewing current guidance about the best candidates for treatment of PTSD with medical cannabis suggested by the CRRB's current guidance (see the last paragraph on page 7).
    - Generally, current guidance suggests only considering medical cannabis for individuals who fail and/or cannot tolerate FDA-approved medications and/or evidence-based psychotherapies for PTSD, when the risks of ongoing severe PTSD symptoms are considered to outweigh the uncertainty about the efficacy and safety of medical cannabis.[2]
- Treatment of PTSD with CBPs is an area of active research (see list of known ongoing trials in **section 8** compiled from trials mentioned by reviewed review articles). The CRRB may consider following up on these trials to assess for new results that could impact recommendations.

8.0 SELECT ONGOING OR RELATED BUT EXCLUDED TRIALS

Studies identified by our literature search referenced several ongoing ETs for CBPs in people with PTSD, which may be monitored for completion and for possible updates to PTSD guidance:

- NCT03518801: https://clinicaltrials.gov/study/NCT03518801. Anticipated study completion September 30, 2024.[41]
- NCT04448808 (THC PTSD-trial): https://clinicaltrials.gov/study/NCT04448808. Anticipated study completion in May 2025.[42] A study protocol is published.[43]
- NCT04080427: https://clinicaltrials.gov/study/NCT04080427. Anticipated study completion in December 2025.[44]
- NCT04550377: https://clinicaltrials.gov/study/NCT04550377. Anticipated study completion in June 2026.[45]
- NCT05269459: https://clinicaltrials.gov/study/NCT05269459. Anticipated study completion in April 2029.[46]

We *excluded* an RCT that compared cannabigerol 25 to 50 mg by mouth daily to placebo among US Veterans with self-reported sleep disturbances, which found no significant between group differences in PTSD severity at 4 weeks.[47] Notably, this trial was excluded due the population not strictly being people with sleep disturbances attributed to PTSD. Its primary objective was to evaluate sleep quality; it also has not yet been published in a peer-reviewed journal (results were posted to the pre-print website, MedRxiv, in September 2023).[47]

9.0 METHODS

We queried 2 major bibliographic databases (Embase and Ovid-Medline) using free-text and controlled vocabulary for key drug, condition, and study design terms. Refer to **Appendix C** for the full search strategy. To target publications published since the last CRRB guidance document was drafted, we searched databases for SRs of experimental studies published between January 1, 2020 and August 19, 2024 using an SR filter developed by McMaster University for Ovid-Medline and an independently derived filter for Embase.[48] Informed by the results of the SR search, we targeted the experimental trials search to publications between January 1, 2023 and August 19, 2024 using a filter for RCTs from the Cochrane Organization.[49]

Targeted studies were experimental (ie, randomized or non-randomized), controlled, trials of cannabis or cannabinoids (plant-based or synthetic) used in patients with PTSD that reported any efficacy or safety outcomes. While we excluded trials of mixed populations with and without PTSD with multiple contributory causes to the target disorder (eg, patients with PTSD and non-PTSD associated sleep disturbances), we elected to include trials targeting patients with PTSD or sub-threshold PTSD who had mean baseline CAPS scores suggestive of PTSD. Additionally, we excluded laboratory trials that exclusively included healthy volunteers, while including laboratory trials with healthy controls without PTSD as long as one study group included patients with PTSD who were allocated to both the CBP and control interventions. Trials with results but without a peer-reviewed publication were considered for inclusion.

A single report author reviewed the results for inclusion by first screening all titles and abstracts, followed by full texts of potentially relevant studies from the SR search. Next, the screening process was repeated for the results from the experimental studies literature search. Studies included/cited by an SR or other review article that was reviewed in full text were also considered for inclusion. Because no reviewed SR or SR and meta-analysis (SRMA) included results from all identified trials, we extracted results from the individual trials, rather than from SR/SRMAs. Select study population characteristics, and efficacy and safety outcomes from each included study were extracted and summarized by a single author. As applicable, we consulted published trial protocols and/or posted study design criterion on clinicaltrials.gov, primarily to assess the trial's eligibility criteria. For trials that did not report a statistical test for major PTSD efficacy outcomes but reported sufficient information to calculate a statistical test, we performed 2-sample t-tests (with equal variance) for differences in mean PTSD symptom scale scores using Stata software. For feasibility, due to time constraints, assessment of the ROB and/or quality of included experimental trials was limited to assessments performed by an SR, when available.

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APPENDIX A – EXPERIMENTAL TRIALS EVIDENCE

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
Bonn-Miller 2021 study population: Adult **US military veterans** (90% male; median 41.2 years) with **chronic (≥ 6 months) PTSD (per DSM-5 criteria) of moderate severity** (baseline CAPS-5 score ≥ 25; mean [SD] PCL-5: 43.7 [15]); **index trauma combat-related: 67.5%; allowed for concurrent stable medication and/or psychotherapy use (details not reported).** No cannabis use allowed within 2-weeks before baseline and during the trial. Exclusion criteria included uncontrolled medical conditions, serious mental illness (eg, psychosis, personability disorder) or family history of psychosis or bipolar disorder, moderate-severe cannabis use disorder (CUD), or use of other illicit substances, among others. Note that 48.6% of screened participants did not meet the trial's eligibility criteria.								
NCT02759185 **Bonn-Miller 2021**[24]	Parallel (phase 1) and cross-over (phase 2; 2-week washout) PC, DB, RCT. Participants randomized to 1 of 3 CBPs or PBO (1:1:1:1) in phase 1, then re-randomized to a different CBP (1:1:1) in phase 2. *Treatment duration: 3 weeks (phase 1, primary outcome); 3 weeks (phase 2)*	Stage 1: 80 (76) Stage 2: 74 (67)	1 of 3 **smoked cannabis** options: 1. **High THC** (12% THC, <0.05% CBD) 2. **Balanced THC/CBD** (7.9% THC, 8,1% CBD) 3. **High CBD** (0.5% THC, 11% CBD) Participants allowed to use cannabis as-needed **up to 1.8 grams/day** (37.8 grams provided for a 3-week period); delivered via metal pipe. Mean (SD) total grams over 3 weeks in phase 1 by group: high THC, 14.6 (10.4); balanced, 8.2 (6.8); high CBD, 14.3 (13.0). During phase 2, participants in the balanced arm used more cannabis (mean total grams [SD]: 17.6 [10.6]) compared to phase 1 and relative to other CBP groups in phase 2 (mean total gram [SD]: high THC, 10.7 [10.9]; high CBD, 9.3 [10.5]).	Placebo (<0.03% THC; <0.01% CBD; during phase 1) Mean (SD) grams/day: 8.4 (10.1)	Mean (SD) change from BL to week 3 (end of phase 1) in total CAPS-5 score **(*primary*)**	High THC: –15.2 (11.0), P<0.0001 Balanced: –8.5 (9.9), P=0.0143 High CBD: –8.4 (10.1), P=0.0181 PBO: –13.1 (12.1), P=0.0002	*No between-group difference: P=0.15*	**Low ROB** per a tool from the Scottish Intercollegiate Guidelines Network[21] **Notes:** • Significant cannabis withdrawal symptoms observed; investigators concluded that cannot rule it out as a contributor to any observed efficacy, and it could have also confounded the results. • Large placebo response reduced the trial's power (trial underpowered)
					Mean (SD) change from new BL [visit 7] to week 3 (end of phase 2) in total CAPS-5 score	High THC: –3.3 (8.2), P<0.2537 Balanced: –11.8 (12.8), P=0.0027 High CBD: –0.48 (9.1), P=0.9941 *Note: BL scores at phase 2 were much lower than at phase 1 BL*	*Significant (P<0.01) differences between high THC and balanced, and between high CBD and balanced groups.*	
					Mean (SD) change from BL to week 3 (end of phase 1) in PCL-5 (patient-reported in past-week)	High THC: –23.5 (16.5), P<0.0001 Balanced: –16.4 (9.1), P=0.0020 High CBD: –12.1 (16.2), P=0.0199 PBO: –14.6 (15.6), P=0.0064	*No between-group difference: P=0.11.*	
					Mean (SD) change from new BL [visit 7] to week 3 (end of phase 2) in PCL-5 (patient-reported in past-week)	High THC: –9.1 (11.0), P=0.164 Balanced: –16.4 (16.0), P=0.0429 High CBD: –5.7 (9.3), P=0.3163 *Note: BL scores at phase 2 were much lower than at phase 1 BL*	*Significant (P=0.02) differences between high CBD and balanced groups.*	
					Mean (SD) change from BL to week 3 in total ISI (insomnia) score	*Phase 1 and phase 2:* Scores significantly reduced from BL in each group (phase 1) and in each group except for high CBD (phase 2); no significant differences between groups.		
					Mean (SD) change from BL to week 3 in IPF (psychosocial functioning) score	*Phase 1 and phase 2:* During phase 1, scores non-significantly increased in high THC and balanced arms, while decreasing slightly in PBO and high CBD groups; during phase 2, small non-significant increases in each group. No significant differences between groups.		

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
					Mean (SD) change from BL to week 3 in IDAS general depression subscale score	*Phase 1:* Significant decreases in scores in each group, with the PBO group exhibiting the smallest numerical decrease; no significant differences between groups. *Phase 2:* Significant decreases in high THC and balanced groups but not the high CBD group, although smaller numerical decreases observed in the high CBD group. Significant difference, but it was not reported between which groups was the difference.		
					Mean (SD) change from BL to week 3 in IDAS social anxiety subscale score	*Phase 1:* Small significantly decreased scores observed in each group; no significant between-group differences. *Phase 2:* Small numerically decreased scores observed in each group, with only the mixed group having a significant decrease. Significant difference, but it was not reported between which groups was the difference.		
					Discontinuation due to AE	*Phase 1 and 2:* n=13 (8.3%)		
					Number reporting any AE	*Phase 1/phase 2:* No significant differences between groups		
					Serious AE, not treatment-related	Balanced: heart palpitations (n=1 [5%]; stage 1); high THC: pulmonary embolism (stage 2 [3.5%]); abscess (n=1 [3.7%]; stage 2)		
					Common AEs (incidence ≥10%)	Cough (12.3%), throat irritation (11.7%), anxiety (10.4%)		
					Treatment-related Two al ideation	*Phase 1:* High CBD (n=1 [5%]); *phase 2:* 1 participant (3.6-5.9%) in each CBP group		
Jetly 2015 study population: Adult **Canadian active-duty military personnel** (**100% male;** median 44 years) with **chronic PTSD** (per DSM-IV-TR criteria; diagnosed ≥2 years prior to trial) **with sleep disturbances** (nightmares or difficulty falling/staying asleep, with relevant CAPS sub-scores ≥5). Allowed to continue mediations at a stable dose, or psychotherapy during the study (details not reported); excluded for significant medical conditions or illicit substance use. No information about prior cannabis use.								
No CT# reported **Jetly 2015**[23]	Cross-over (2-week washout), PC, DB, RCT Participants randomized (1:1 to starting with nabilone or placebo) *Treatment duration: 7 weeks, including 2 weeks at the target nabilone/placebo dose*	?? (10); 1 participant completed only 1 phase of the study	Nabilone, 0.5–3 mg 1 hour before bedtime; titrated weekly to response (nightmare suppression) and tolerability, with the dose at 5 weeks continued for the last 2 trial weeks. Mean dose: 1.95 ± 0.9 mg	Placebo Mean dose: 2.78 ± 0.7 mg	Mean (SD) change from BL to 7 weeks in CAPS recurring/distressing dream sub-item score *Accounted for frequency and intensity, which are both 0-4 Likert scale items but it's unclear how the scores were exactly calculated.*	Nabilone: –3.6 (2.4) Placebo: –1.0 (2.1)	*Significant between-group difference (P=0.03).* *Similar effect observed when calculation performed separately for frequency and intensity.*	**High ROB** per a tool from the Scottish Intercollegiate Guidelines Network: lacked sufficient reporting about randomization, allocation concealment, baseline characteristics; and did not use statistical methods to address cross-over analysis, while also reporting all results together (not by treatment period).[21]
					Mean (SD) change? (*not well described*) in CAPS difficult falling/staying asleep sub-item score	"No effect observed" (details not reported)		
					Mean (SD) change from BL to 7 weeks in CGI-C (1=very much improved; 7=very much worse)	Nabilone: 1.9 (1.1) Placebo: 3.2 (1.2)	*Non-significant difference, numerically favoring nabilone (P=0.05)*	

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
					Mean (SD) change in well-being score from BL to 7 weeks (highest well-being = 100 score)	Nabilone: 20.8 (22.1) Placebo: –0.4 (20.6)	*Significant between-group difference (P=0.04)*	
					Number (%) reporting no distressing dreams in the past week (at week 7)	Nabilone: 4 (44%) Placebo: 0 (0%)	*Statistical test not reported*	
					% with treatment-related AE	Nabilone: 50% Placebo: 60%	Most common AEs with nabilone: dry mouth (n=6), headache (n=4)	
					% with withdrawal due to AE	Nabilone: 0% Placebo: 0%		
Walsh 2023 target study population: **Canadian** adults (83.3% male) with **chronic** (≥6 months), **moderate severity** (PCL-5 score ≥ 40 at BL), **treatment-resistant** (failure of ≥1 medication or psychotherapy for PTSD) PTSD, who were receiving a stable medication or psychotherapy regimen; excluded participants with severe medical illness, a personal or family history of psychosis or bipolar disorder, borderline personability disorder, depression with psychosis, cannabis use disorder or other substance use disorder.								
NCT02517424 **Walsh 2023**[25,34]	Designed as a parallel (phase 1) and cross-over (phase 2; 2-week washout) PC, DB, RCT, but *switched to an uncontrolled, with-in subject analysis.* Designed to include 2 phases: phase 1, participants randomized to 1 of 2 CBPs or PBO (1:1:1) , then re-randomized to a CBP in phase 2. However, due to low enrollment, changes to measure within-participant change from BL to end of active treatment. *Treatment duration: 3 weeks*	6 (5) Targeted enrolling 42.	1 of 2 **vaporized dried cannabis** options: 1. **High THC** (10±2% THC, <1% CBD) 2. **Balanced THC/CBD** (10±2% THC, 10±2% CBD) Participants allowed to use cannabis as-needed **up to 2 grams/day.** *Phase 1:* high THC (n=1); balanced (n=4) (BL to week 3 used for within-subject analysis) *Phase 2:* high THC (n=1) (week 5 to week 8 used for within-subject analysis)	Placebo (<1% THC, <1% CBD) *Phase 1:* placebo (n=1); this participant received high THC in phase 2	*With-in subject* difference in mean (SD) CAPS-5 total scores between BL and week 3 (**primary**)	All active treatment (balanced or high THC): BL/week 5 = 39.0 (5.9) Week 3/8 = 30.7 (11.2)	*Numerical differences not statistically significant (two-sided P = 0.11; 1-sided P=0.06)* *Similar results observed from a with-in subject analysis of PCL-5 scores (although scores on this scale were prorated for 2 participants due to missing data). Authors considered this to be a medium-sized effect.*	**No ROB by a reviewed SR** **Note**: This study struggled with recruitment and failed to achieve the target number of participants (thus, it is underpowered). Additionally, a participant was not exposed to all study groups in the original design, and analysis of the placebo group was not feasible. Switched to a within subject analysis due to poor enrollment. Randomization was not successful due to poor enrollment. **Authors consider the results to be exploratory.**

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
NCT03248167 study population: US adults (18-70 years old; **63.3% female**) **with moderate-to-severe alcohol use disorder (with ≥ 6 heavy drinking days in the 30 days before baseline) and PTSD** (per CAPS-5 criteria) **or subthreshold PTSD** (ie, meeting PTSD criteria A, F, G, H and ≥ 6 symptoms among criterion B-E). No cannabis use was allowed during the study; and participants with severe medical conditions including significant liver function impairment, schizophrenia or schizoaffective disorder, bipolar disorder, serious suicidality, recent trauma in the past 30 days, mild cannabis use disorder or moderate-to-severe other SUD or receiving current treatments for AUD (except for psychosocial treatment started ≥ 3 months prior) or psychotherapy that started within the prior 3 months were excluded. Excluded for use of cannabinoids or serotonergic medications.								
NCT03248167 Limited publication on clinicaltrials.gov[26]	Parallel, PC, DB, RCT *Treatment duration: 6 weeks*	95 (30/21; 65 participants failed screening or withdrew prior to starting the trial treatments; of the 30 who started treatment, 21 (70%) completed the trial)	CBD 600 mg daily, n=17	Placebo, n=13	Mean (SD) number of drinks per day (primary)	<u>Baseline:</u> CBD, 4.5 (2.7); PBO, 5.4 (2.7) <u>Week 4:</u> CBD, 1.9 (2.2); PBO, 2.2 (2.3) <u>Week 6:</u> CBD, 2.5 (2.2); PBO, 2.8 (2.3)	*Generally, results for secondary drinking-related outcomes (eg, % of heavy drinking days; % with no heavy drinking days; % of days abstinent) exhibited similar patterns to this outcome*	**No ROB by a reviewed SR** **Note:** The trial's primary objective was to assess the impact of CBD for the treatment of alcohol use disorder among people with co-morbid PTSD. While additional secondary alcohol use related outcomes were reported, we did not extract them. No statistical comparisons reported, and no study protocol was posted to clinicaltrials.gov.
					Mean (SD) PCL-5 total score (co-primary)	<u>Baseline:</u> CBD, 42.1 (13.9); PBO, 49.2 (13.8) <u>Week 4:</u> CBD, 19.9 (15.7); PBO, 29.9 (16.8) <u>Week 6:</u> CBD, 26.6 (18.5); PBO, 26.9 (17.7)	*Authors did not report statistical tests. We performed 2-sample t-tests for differences in the mean PCL-5 scores at baseline and week 6, which found no significant differences (P=0.1755 at baseline, and P=0.9119 at week 6).*	
					Trial withdrawals (reason)	CBD: n=5/17 (29.4%); n=2 (patient withdrawal); n=2 (COViD-19 pause); n=1 (lost to follow-up) PBO: n=4/13 (30.8%); n=2 (patient withdrawal); n=1 (provider decision); n=1 (COVID-19 pause); n=0 (lost to follow-up)		
					Mortality or SAE	0 (0%) in both groups		
					Other AEs with incidence ≥ 10% in either study arm	Any AE: CBD, 88.2%; PBO, 76.9% Diarrhea: CBD, 17.7%; PBO, 7.7% Headache: CBD, 11.8%; PBO, 0% Nausea: CBD, 17.7%; PBO, 0% Drowsiness: CBD, 35.3%; PBO, 30.8% Fatigue: CBD, 11.8%; PBO, 7.7% Increased hunger: CBD, 11.8%; PBO, 7.7% Nightmares: CBD, 5.9%; PBO, 15.4% Weight gain: CBD, 17.7%; PBO, 15.4%		
					Any psychiatric AEs	Anxiety: CBD, 0%; PBO, 7.7% Feeling overwhelmed: CBD, 5.9%; PBO, 0% Lack of motivation: CBD, 5.9%, PBO, 0%; Suicidal ideation: CBD, 5.9%; PBO, 0%		

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
Bolsoni 2022 study population: **Adults** (18-60 years; **75.8% female**) **from Brazil with PTSD** (per DSM-5 criteria, confirmed with a structured clinical interview) from **sexual abuse (42.4%) or non-sexual trauma (57.6%; including various traumas, not necessarily combat/military related)** without psychiatric conditions (except depression or anxiety, that were allowed) and drug abuse/dependence. Patients had mean baseline PCL-5 scores of 52.5 (CBD) or 54.1 (PBO); maximum score is 80, and 51.5% were taking a psychiatric medication. A higher proportion of patients in the CBD arm had a mood or anxiety disorder at BL (CBD: 88.2% vs PBO: 37.5%).								
No CT# reported **Bolsoni 2022a,b**[27,28]	Parallel, PC, DB, RCT Randomized (by minimization) 1:1, with matching for sex, age, BMI, and symptom severity. Study involved a behavioral test (in 3 sessions with 1 week between sessions), with outcomes measured before and after the test. The first session involved recording the patient's trauma and imagining the trauma, then in session 2 and 3, the patient listened to their recorded trauma report and imagined it. *Duration: Single dose study, with outcomes measured before/after the trauma recordings/recall, starting 90 min after the CBD/placebo administration. Participants repeated the tests 1 week later without CBD/placebo.*	33 (33? – not reported) Sexual trauma subgroup: CBD, n=7; PBO, n=7; Non-sexual trauma subgroup: CBD, n=10; PBO, n=9).	**CBD 300 mg** dissolved in corn oil and packed in gelatin capsules, **<u>administered once</u> ~90 minutes before a behavioral test during session 2**	Matched placebo (corn oil only)	VAMS anxiety mean (SD) score before/after behavioral test	*Day 2 (date CBD/PBO given):* <u>Before</u>: CBD, 40.3 (14.6); PBO, 36.8 (14.9) <u>After</u>: CBD, 54.9 (15.1); PBO, 55 (12.6); P<0.001 vs before *Day 3 (1 week after CBD/PBO):* <u>Before</u>: CBD, 45.4 (7.6); PBO, 44.4 (14.8) <u>After</u>: CBD, 59.1 (15.0); PBO, 59.4 (15.5); P<0.001 vs before	*VAMS score results show significantly (P<0.001) increased patient-reported anxiety, decreased sedation, and increased discomfort in both treatment groups after the recall test compared to before; this was observed in both session 2 and 3. Authors suggest this validates their model.* *The difference with CBD vs PBO was observed on cognitive impairment, for which the increased impairment following recall was attenuated in the CBD group vs PBO group (P=0.03 during session 2; and P=0.04 during session 3).* *<u>In a separate report (inferred as a post-hoc analysis),</u> investigators explored the impact of type of trauma (sexual vs non-sexual) on these results. In the non-sexual trauma group, CBD significantly attenuated anxiety and cognitive impairment vs PBO, whereas this was not observed in the sexual trauma group. (P=0.01 and P=0.02 for*	**Note:** No corrections for multiple comparisons. An effect of CBD on cognition was not initially hypothesized, thus authors suggest considering their results to be preliminary. Depressive or anxiety disorder comorbidities that were more common in people who received CBD could have confounded the results.
					VAMS sedation mean (SD) score before/after behavioral test	*Day 2 (date CBD/PBO given):* <u>Before</u>: CBD, 58.5 (10.4); PBO, 54.3 (14.5) <u>After</u>: CBD, 42.2 (14.8); PBO, 42.0 (13.6); P<0.001 vs before *Day 3 (1 week after CBD/PBO):* <u>Before</u>: CBD, 47.9 (16.1); PBO, 42.8 (14.6) <u>After</u>: CBD, 40.6 (15.0); PBO, 39.1 (16.3); P<0.001 vs before		
					VAMS cognitive impairment mean (SD) score before/after behavioral test	*Day 2 (date CBD/PBO given):* <u>Before</u>: CBD, 45.4 (11.7); PBO, 43.4 (11.6) <u>After</u>: CBD, 49.2 (13.0); PBO, 53.4 (15.8); P<0.001 vs before *Day 3 (1 week after CBD/PBO):* <u>Before</u>: CBD, 43.6 (11.2); PBO, 43.9 (12.8) <u>After</u>: CBD, 45.8 (12.8); PBO, 52.2 (14.6); P<0.001 vs before		

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
					VAMS discomfort mean (SD) score before/after behavioral test	*Day 2 (date CBD/PBO given):* Before: CBD, 37.7 (11.8); PBO, 40.9 (11.8) After: CBD, 46.9 (12.2); PBO, 49.8 (11.2) *Day 3 (1 week after CBD/PBO):* Before: CBD, 41.1 (13.4); PBO, 39.2 (13.8) After: CBD, 48 (13.6); PBO, 48.9 (13.3)	*the phase x group x trauma interaction).*	
					Changes in BP, HR, and salivary cortisol before/after behavioral test	No significant impact of treatment (CBD vs PBO) or timing (before/after test) on salivary cortisol, HR, or DBP. Only significant effect was increased SBP following recall in session 2.		
Rabinak 2020 study population: Right-handed **US adults (50% female** overall; 84.6% and 60% female in the PTSD THC- and PBO-treated subgroup) **with or without prior trauma exposure**. The PTSD subpopulation had PTSD per CAPS-5 diagnostic criteria or per a CAPS-5 severity score ≥ 25; note that the TEC subpopulation had CAPS-5 scores <25 or did not meet criteria for PTSD. In the PTSD subpopulation, participants in each treatment group were well-balanced with respect to baseline sociodemographic characteristics and PTSD severity. Regarding prior cannabis use, 26.3% of the PTSD group had used cannabis in the past 30 days (30% of the THC-treated group and 22.2% of the PBO-treated group).								
NCT02069366[a] **Rabinak 2020[35]**	Parallel, PC, DB, RCT Included participants with PTSD, or that were trauma-exposed without PTSD (TEC) or healthy controls (HC); a subset of each subpopulation were randomized to THC or PBO. Participants completed a threat processing task involving the viewing of photographs of faces considered threatening or non-threatening (eg, compare happy vs fearful face; and happy faces vs shapes) that is proven to create threat-related amygdala responses. *Treatment duration: One-time treatment administration*	86 (71; including 19 in the PTSD subgroup)	Dronabinol 7.5 mg orally **one-time** 120 minutes before fMRI scan	Matched placebo (dextrose only)	fMRI activation results during threat processing test, measured during peak THC/PBO effect	• THC vs PBO overall: *decreased* bilateral basolateral (BL) and superficial (SF) amygdala activation (P<0.05) • THC vs PBO in PTSD group: *increased* medial prefrontal cortex (mPFC)/adjacent rostrate cingulate cortex (rACC) activation (P=0.009); no difference between THC and PBO was observed in the other groups • THC vs PBO in PTSD group: *decreased* amygdalostriatal [AStr] response during the threat condition (P=0.045); this was not observed in the other groups	*Rabinak et al 2020 conclusion: "Consistent with previous findings in healthy adults, we found that, within the PTSD group, THC attenuated amygdala activation, increased mPFC/rACC activation, and increased corticolimbic functional connectivity to threat compared to PBO"(page 237); "These preliminary data suggest that THC modulates threat-related processing in trauma-exposed individuals with PTSD"*	**Unclear ROB (some concerns) per SR using the Cochrane ROB tool as of 2020.** The trial was rated as having an unclear ROB for the domains of random sequence generation, allocation concealment and other (for being a laboratory study), whereas it was rated as having a low ROB for the domains of blinding of participants, personnel and outcome assessors; and for attrition bias and selective reporting.[38]

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result	ROB per SR
					fMRI functional connectivity results during threat processing test, measured during peak THC/PBO effect	• <u>THC vs PBO overall:</u> *increased* mPFC/ACC–amygdala functional connectivity (P=0.006) • <u>THC overall in threat vs non-threat conditions:</u> during non- threat condition, THC increased mPFC/rACC connectivity with the BL SF (vs PBO; P=0.002); and THC *decreased* mPFC/rACC connectivity with the right SF during threat (vs non-threat; P=0.030) • <u>THC in PTSD group vs other group:</u> *increased* mPFC/rACC connectivity with right SF vs TEC (P=0.009) and HC (P=0.008) groups • <u>THC vs PBO in PTSD group:</u> *increased* mPFC/rACC connectivity with right SF (P=0.005); not observed in the other groups	**Note:** This trial was not designed to assess the therapeutic efficacy of dronabinol. Corrected for multiple comparisons (Rabinak 2020). When extracting outcomes, we focused on reported comparisons of THC vs PBO within the PTSD group.
					Mortality, SAE, or any AE, per clinicaltrials.gov (for the overall trial)	0% in each treatment group	
					Number of participants and reasons for exclusion from the data analysis	15 total patients excluded (17.4% of those randomized; receipt of THC/PBO condition not specified), for reasons of: brain abnormality (n=1), ineligibility (n=3; eg, recent mood disorder diagnosis), loss to follow-up (n=1), incomplete fMRI images (n=6), and poor behavioral performance (n=6)	

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
Pacitto 2022 study population: Right-handed **US adults (aged 20-45 years; 56% female** overall and 90% female/54.5% female in the THC/PBO-treated groups of the PTSD group) **with or without prior trauma exposure**. The PTSD subpopulation had PTSD per CAPS-5 diagnostic criteria (mean BL total severity score: 33.6 in the THC-treated group and 35 in the PBO-treated group); note that the TEC subpopulation had been exposed to trauma, but did not meet CAPS-5 diagnostic criteria (mean CAPS-5 total severity scores of <4). Participants were excluded for a history of primary comorbid anxiety disorder, schizophrenia, bipolar disorder, current suicidal ideation, personality disorder, or current alcohol/drug abuse/dependence; recent use of several medications including fluoxetine or current exposure-based PTSD therapy was also exclusionary. Groups were well balanced with respect to BL reappraisal and suppression sub-scores on the Emotional Regulation Questionnaire. Regarding prior cannabis use, 28.5% of the PTSD group had used cannabis in the past 30 days (30% of the THC-treated group and 27.3% of the PBO-treated group).								
NCT02069366[a] **Pacitto 2022**[30]	Parallel, PC, DB, RCT Included participants with PTSD, or that were trauma-exposed without PTSD (TEC) or healthy controls (HC); a subset of each subpopulation were randomized to THC or PBO. Participants completed an Emotion Regulation Task that involved three conditions based on the type of image viewed (neutral or unpleasant) and use of cognitive strategies: (1) 'maintain neutral' = regular processing of a neutral image; (2) 'maintain negative' = regular processing of an unpleasant image; and (3) 'reappraisal negative' = processing of a negative image, participants used a cognitive strategy intended to lessen the arousal invoked by the unpleasant image. *Treatment duration: One-time treatment administration*	131 (57 randomized; 51 in analysis)	Dronabinol 7.5 mg orally **one-time** 120 minutes before fMRI scan	Matched placebo (dextrose only)	fMRI activation results during the Emotional Regulation Task, measured during peak THC/PBO effect	• THC vs PBO overall: *increased* right dmPFC (dorsomedial prefrontal cortex) activation in *maintain neutral* (but not in maintain negative or reappraisal negative); P=0.004 • THC vs PBO in PTSD group: During PBO treatment, *reduced* lower left angular gyrus activation *vs TEC group* (P<0.001); however, during THC treatment, no significant differences in left angular gyrus (or dmPFC) activation *vs the TEC group* • THC vs PBO in PTSD group: No differences in left angular activation (P>0.05) • THC vs PBO in PTSD group: *increased* cerebellar activity in *maintain neutral* (P=0.013). Note that *compared the TEC group*, the PTSD group had increased activation of the cerebellum during *maintain neutral* and *reappraisal negative*, but these differences were not observed among those who received THC.	*Pacitto et al 2022 conclusions: "…the present study demonstrates that an acute, low dose of THC improved the efficacy of cognitive reappraisal among trauma-exposure individuals and modulated activity in brain regions involved in emotional processing and regulation. Individuals with PTSD were found to have lower angular gyrus activation at baseline compared to TEC, and THC normalized this discrepancy…"(page 8) "Compared to PBO, THC also increased cerebellar activation during exposure to neutral images in individuals with PTSD. Lastly, in participants that received THC, greater posterior cingulate cortex (PCC)/precuneus activation during reappraisal was associated with less self-reported negative affect…" (page 1)*	**No ROB by a reviewed SR (although the bias for another sub-study of this trial was evaluated)** **Note:** This trial was not designed to assess the therapeutic efficacy of dronabinol. Corrected for multiple comparisons. When extracting outcomes, we focused on reported comparisons of THC vs PBO within the PTSD group, as feasible.

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result	ROB per SR
					Participants subjective ratings directly following the Emotional Regulation Task	*No presented results contrasted the effects of THC vs PBO among the PTSD group only*. Generally, PBO recipients were more aroused by negative images compared to THC recipients among the total population (inferred as PTSD+TEC). The increased negative affect during reappraisal negative vs maintain neutral was less among THC participants vs PBO recipients.	
					Correlation between fMRI image and subjective ratings	The only statistically significant finding was a negative correlation (r=–0.524; P=0.007) between negative affect ratings and left (posterior cingulate cortex) PCC/precuneus activation *among all THC recipients.*	
					Number of participants and reasons for exclusion from the data analysis	6 patients total excluded (10.5% of those randomized; receipt of THC/PBO condition not specified), for reasons of: brain abnormality (n=1), ineligibility (n=3; eg, recent mood disorder diagnosis), and incomplete fMRI images (n=2).	

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
Zabik 2023 study population: Right-handed **US adults (ages 21-45; 49.3% female overall**, and 68.4% in the PTSD group) **with or without prior trauma exposure**. The PTSD subpopulation met CAPS-5 criteria for PTSD or had a total CAPS-5 score ≥ 25 (mean BL total severity score was 34.4 in the THC group and 34.2 in the PBO group) . Participants were excluded for a history of primary comorbid anxiety disorder, schizophrenia, bipolar disorder, current suicidal ideation, personality disorder, or current alcohol/drug abuse/dependence; recent use of several medications including SSRIs, among others, or current exposure-based PTSD therapy was also exclusionary.								
NCT02069366[a] **Zabik 2023**[31]	Parallel, PC, DB, RCT Included participants with PTSD, or that were trauma-exposed without PTSD (TEC) or healthy controls (HC); a subset of each subpopulation were randomized to THC or PBO. Participants completed a validated Pavlovian fear-extinction protocol. On day 1, participants completed fear conditioning (16 minutes; ie, learning a conditioned stimulus [CS] with [CS+] or without [CS-] an unconditioned stimulus [US]) at a computer. Then, on day 2 they completed extinction learning (11 minutes; ie, learning a CS without the US = CS+E) during the fMRI scan. Finally, on day 3, the completed extinction recall and fear renewal (16 minutes; ie, random order of CS+E, CS+US, or CS-) during an fMRI scan. Surrounding scans, patient-reported subjective distress was recorded (measured in increments of 10 units, where 0 = no anxiety and 100 = worst ever anxiety). *Treatment duration: One-time treatment administration, with effects measured*	86 (71 included in analysis)	Dronabinol 7.5 mg orally **<u>one-time</u>** 120 minutes before fMRI scan and extinction learning on day 2	Matched placebo (dextrose only)	fMRI activation and interaction with time (early vs late; early = second trial of stimulus [for fear acquisition] or first trial [for extinction learning, recall, and fear learning]; late = the 20th [last] trial of the stimulus)	• <u>THC vs PBO in PTSD group, *extinction learning*</u>: no differences in activation/time interaction effects • <u>PTSD group vs TEC group, both who had received THC, *extinction learning:*</u> Increased vmPFC activation early compared to late (P=0.017) • <u>All who received THC, *extinction recall:*</u> greater right hippocampus activation early (vs late; P=0.013) • <u>THC vs PBO in PTSD group, *fear renewal:*</u> Greater left amygdala activation during early CS + E compared to CS- (P=0.031)	*Zabik et al conclusions: "During extinction learning, individuals with PTSD given THC had greater vmPFC activation than their THC counterparts. During a test of the return of fear (i.e., renewal), HC and individuals with PTSD given THC had greater vmPFC activation compared to TEC. Individuals with PTSD given THC also had greater amygdala activation compared to those given PBO. WE found no effects of trauma group or THC on behavioral fear indices during extinction learning, recall, and fear renewal" (page 1)*	**No ROB by a reviewed SR (although the bias for another sub-study of this trial was evaluated)** **Note:** This trial was not designed to assess the therapeutic efficacy of dronabinol. Corrected for multiple comparisons. When extracting outcomes, we focused on reported comparisons of THC vs PBO within the PTSD group, as feasible. This sub-study was likely the primary trial results based on the title on clincialtrials.gov, among the publications with the same registered trial number.
					Expectancy ratings (ie, patient-report of whether they expected to hear the loud noise [US])	Expectancy ratings did not significantly vary by drug group (THC or PBO) or trauma group type		
					Subjective distress ratings	Subjective distress did not vary by time, trauma group, or drug group		
					Number of participants and reasons for exclusion from the data analysis	15 patients total excluded (17.4% of those randomized; receipt of THC/PBO condition not specified), for reasons of: brain abnormality (n=1), ineligibility (n=6; eg, recent mood disorder diagnosis), and incomplete fMRI images (n=7), and loss to follow-up (n=1).		

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result		ROB per SR
NCT05132699 study population: US **adults** (18-65 years**; 62% male) with PTSD** (confirmed by CAPS-5) who were on a stable medication regimen for at least 4 weeks prior and were willing to participate in PE. Randomization was stratified PTSD severity and type of population (military vs not). Participants were excluded for major medical comorbidities; ongoing use of medications known to interact with CBD; current ongoing PTSD therapy, use of opioids, methamphetamine, cocaine or cannabis; severe drug or alcohol abuse at the discretion of the provider; and/or psychosis, mania or suicidal ideation requiring hospitalization.								
NCT05132699 Limited publication on clinical trials.gov with a published study protocol[7,32]	Parallel, PC, DB, pilot RCT of CBD/PBO as an adjunct to prolonged exposure (PE) psychotherapy PE: 10, 90-minute sessions of manualized, daily PE over 14 days (excluding weekends). *Treatment duration: 18 days (to assess benefit; outcome measures repeated 1-month after the last PE session (to assess maintenance of benefit).*	21 (18)	CBD (Epidiolex) 250 mg twice daily (in AM and evening after high fat meals) x 18 days, started 3 days before PE therapy	Matched PBO	Mean (SEM) CAPS-5 score at BL and approximately day 45 (1-month follow-up at end of PE)	BL: CBD, 42 (2.6); PBO, 43 (3.1) 1-month follow-up: CBD, 15.9 (3.4); PBO, 10.0 (3.4)	*Authors did not report statistical tests. We performed 2-sample t-tests for differences in the mean CAPS-5 scores at baseline and 1-month follow-up, which found no significant differences (P=0.9825 at baseline, and P=0.3390 at follow-up).*	**No ROB by a reviewed SR** Note: No statistical tests reported, as results are those posted to clinicaltrials.gov and not yet published in a journal. Study was not powered for hypothesis test since it was considered a pilot/feasibility trial. Trial protocol reports planning to assess efficacy at other timepoints (eg, on last day of PE) and biological outcomes (ie, saliva cortisol levels, endogenous cannabinoid levels in blood), which are not reported to clinicaltrials.gov. Complete quality review had not completed when results were extracted from clinicaltrials.gov.
					Mean (SEM) PCL-5 score at BL and approximately day 45 (1-month follow-up at end of PE)	BL: CBD, 50.9 (0.8); PBO, 52.0 (0.9) 1-month follow-up: CBD, 20.3 (7.7); PBO, 27.2 (8.1)	*Authors did not report statistical tests. We performed 2-sample t-tests for differences in the mean PCL-5 scores at baseline and 1-month follow-up, which found no significant differences (P=0.9062 at baseline, and P=0.6457 at follow-up).*	
					Mean (SEM) PHQ-9 (depression) score at BL and approximately day 45 (1-month follow-up at end of PE)	BL: CBD, 14.8 (0.5); PBO, 15.4 (0.5) 1-month follow-up: CBD, 5.7 (2.4); PBO, 7.1 (2.5)		
					Mortality and SAE	Mortality: 0 (0%) in both groups SAE: 0 (0%) in both groups		
					Other AEs	Overall rate of any AE: CBD, 10/11 (90.9%); PBO, 7/10 (70.0%) AEs ≥10% in either group: GI issues (diarrhea, cramps, nausea): CBD, 36.4%; PBO, 20% Sensation from drug: CBD, 0%; PBO: 20% Emotional problems: CBD, 27.3%; PBO, 10% Sleep disturbance (increased nightmares and insomnia): CBD, 36.4%; PBO, 0%		
					Trial withdrawals (reason for withdrawal not reported)	CBD: 3/11 (27.3%) PBO: 0/10 (0.0%)		

*Table A1. Summary of the Study Design and **Select** Efficacy and Safety Outcomes from Included Experimental Trials among People with PTSD*

Study: CT#, First Author, Publication Year	Design and duration	Participants recruited (completed)	CBP Intervention(s)	Comparator	Outcome	Result	ROB per SR

Abbreviations: AE, adverse event; BL, baseline or bilateral; CAPS-5, Clinician Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CBD, cannabidiol; CBP, cannabis/cannabinoid-based product; DB, double-blind; fMRI, functional magnetic resonance imaging; dmPFC, dorsomedial prefrontal cortex; HC, healthy control; IDAS, Inventory of Depression and Anxiety; IPF, Inventory of Psychosocial Functioning; ISI, Insomnia Severity Index; NCT, national clinical trial; PBO, placebo; PC, placebo controlled; PCL-5, PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PTSD, post-traumatic stress disorder; rACC, rostral anterior cingulate cortex; RCT, randomized controlled trial; ROB, risk of bias; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; SR, systematic review; TEC, trauma-exposed control; THC, (delta-9)-tetrahydrocannabinol

[a]Although different participant numbers are reported, the publications Rabinak 2020, Pacitto 2022, and Zabik 2023 are apparently part of the same registered trial (of which Zabik 2023 may be the primary larger trial) based on the registered trial number. Because they reported different numbers of participants, we describe their study populations separately, even though it is possible that participants were represented in more than one of the publications. We infer that most described eligibility criteria applied to each sub-trial.

APPENDIX B – NATIONAL ACADEMIES LEVEL OF EVIDENCE CATEGORIES

Historically, the CRRB has assigned level of evidence (LOE) ratings to graded statements using LOE categories for therapeutic recommendations from the 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) cannabis evidence report.[50] Refer to **Table B1** for characteristics of each NASEM LOE category.

Table B1. Levels of Evidence for Therapeutic Effects from the 2017 NASEM Cannabis Report

Conclusive Evidence
• "There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[50] • "For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitation of the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence" (page 7).[50]
Substantial Evidence
• "There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 7).[50] • "For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence" (page 7).[50]
Moderate Evidence
• "There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8). • "For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence." (page 8).[50]
Limited Evidence
• "There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[50] • "For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors" (page 8).[50]
No or Insufficient Evidence
• "There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest" (page 8).[50] • "For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors" (page 8).[50]

Abbreviations: NASEM, The National Academies of Sciences, Engineering, and Medicine

APPENDIX C – LITERATURE SEARCHES

Table C1. Ovid-Medline Literature Search Strategy for Systematic Reviews and Experimental Trials

Database(s): Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily August 15, 2024 Date of Search: August 19, 2024		
#	**Searches**	**Results**
1	exp stress disorders, traumatic/	48284
2	(PTSD or post-traumatic stress or posttraumatic stress).ti,ab,kw,kf.	54465
3	1 or 2	68415
4	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	40369
5	(mari?uana or pot or hash* or bhang* or gan?a* or weed* or hemp*).ti,ab,kw,kf.	93131
6	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	71658
7	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	706
8	(nabilone or dronabinol or marinol or syndros or cesamet or epid#olex or nabiximol* or Sativex or bedrocan or bedrobinol or bedica or bediol or bedrolite or dexanbinol).ti,ab,kw,kf.	1318
9	4 or 5 or 6 or 7 or 8	160583
10	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "systematic review"/ or ((sytematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	544909
11	(MEDLINE or Embase or Pubmed or systematic review).tw. or meta analysis.pt.	563088
12	10 or 11	675734
13	3 and 9 and 12	84
14	(randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1669481
15	3 and 9 and 14	121
16	limit 13 to yr="2020 -Current"	53
17	limit 15 to yr="2023 -Current"	20

Table C2. Embase Literature Search Strategy for Systematic Reviews and Experimental Trials

Embase Session Results

Date of Search: August 19, 2024

#	Searches	Results
1	'posttraumatic stress disorder'/exp	88,418
2	ptsd:ti,ab,kw OR 'post-traumatic stress':ti,ab,kw OR 'posttraumatic stress':ti,ab,kw	69,449
3	#1 OR #2	97,181
4	'cannabinoid'/exp OR 'cannabis use'/exp OR 'cannabis smoking'/exp OR 'cannabis addiction'/exp	109,477
5	mari?uana:ti,ab,kw OR pot:ti,ab,kw OR hash*:ti,ab,kw OR bhang*:ti,ab,kw OR gan?a*:ti,ab,kw OR weed*:ti,ab,kw OR hemp*:ti,ab,kw	115,262
6	tetrahydrocannab*:ti,ab,kw OR cannabi*:ti,ab,kw OR thc:ti,ab,kw OR cbd:ti,ab,kw OR cbn:ti,ab,kw OR cbg:ti,ab,kw OR cbc:ti,ab,kw OR thcv:ti,ab,kw OR cbdv:ti,ab,kw OR cbcv:ti,ab,kw OR cbgv:ti,ab,kw OR thca:ti,ab,kw OR cbda:ti,ab,kw OR cbga:ti,ab,kw OR cbna:ti,ab,kw	109,307
7	thc:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	911
8	nabilone:ti,ab,kw OR dronabinol:ti,ab,kw OR marinol:ti,ab,kw OR syndros:ti,ab,kw OR cesamet:ti,ab,kw OR epid?olex:ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw OR bedrocan:ti,ab,kw OR bedrobinol:ti,ab,kw OR bedica:ti,ab,kw OR bediol:ti,ab,kw OR bedrolite:ti,ab,kw OR dexanabinol:ti,ab,kw	2,098
9	#4 OR #5 OR #6 OR #7 OR #8	246,088
10	cochrane*:jt OR 'systematic review*':jt OR 'meta analysis'/exp OR 'systematic review'/exp OR ((systematic* NEAR/3 review*):ti,ab,kw) OR ((systematic* NEAR/2 search*):ti,ab,kw) OR 'meta analys*':ti,ab,kw OR metaanalys*:ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)	798,388
11	#3 AND #9 AND #10	187
12	#3 AND #9 AND #10 AND [2020-2024]/py	128
13	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	3,384,976
14	#3 AND #9 AND #13	413
15	#3 AND #9 AND #13 AND [2023-2024]/py	71