COLLEGE OF PHARMACY
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EVIDENCE REVIEW:

Experimental Controlled Trials on the Treatment of PTSD with Cannabis-based Products

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I have no conflicts of interest to disclose

BRIEF EVIDENCE REPORT OBJECTIVE & METHODS

- **Objective:**
  - Summarize recent experimental evidence for the use of cannabis- or cannabinoid-based products (CBPs) for PTSD using a hierarchy-of-evidence approach
  - Assist the CRRB with updating guidance

- **Methods:**
  - Searched for SRs of experimental controlled trials (ECTs) published since 2020, and ECTs (eg, RCTs) published since 2023*
  - Included ECTs of any design with:
    - ≥1 study group with confirmed PTSD, or with mean PTSD symptom scale scores (ie, CAPS) suggestive of PTSD
    - Treatment with CBPs (natural or synthetic) for any duration;
    - Any efficacy or safety outcome
  - Summarized select efficacy and safety results from ECTs
  - Extracted ROB ratings from SRs[1,2]
  - Performed limited basic statistical tests for trials with only descriptive results

*Narrowed RCT search dates to 2023-2024 based on the search dates of SRs

Abbreviations: CAPS, Clinician-Administered PTSD Scale; CBP, cannabis- or cannabinoid-based product; CRRB, Utah Cannabis Research Review Board; ECT, experimental controlled trial; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; ROB, risk of bias; SR, systematic review

INCLUDED TRIALS

- 7 placebo-controlled RCTs (8 published records, 2 limited result records), with **3 approaches:**
  1. Multiple CBP doses for the symptomatic treatment of PTSD (N=4)[3,4,5,6]
  2. Acute effects of a single CBP dose in a laboratory setting (N=2)[7-11]
  3. CBP as an adjunct to massed prolonged exposure (PE) therapy (N=1)[12]

- Small trials, including ~209 total participants (~130 received a CBP)

- Trial populations varied and were under-described; generally, trials included:
  - Adults
  - Primarily male (approach 1 & 3) or female (approach 2)
  - PTSD per DSM-5 criteria, except for Jetly et al 2015 (used DSM-4-TR)
  - PTSD of at least moderate severity
  - Participants without serious or severe psychiatric comorbidities, including substance use disorders (with some exceptions for CUD or AUD)

Abbreviations: AUD, alcohol use disorder; CBP, cannabis or cannabinoid-based product; CUD, cannabis use disorder; DSM-4/5, *Diagnostic and Statistical Manual of Mental Health Disorders* – Fourth or Fifth Edition; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; TR, text revision

OVERVIEW OF MULTI-DOSE SYMPTOMATIC TRIALS (APPROACH 1)

Trial and design	Population (total/completed n)	Approx. tx. length
Jetly et al 2015[3] No CT# reported *Cross-over*, DB, PC RCT	• Adults (100% male) with **chronic PTSD and *distressing nightmares and difficulty falling/staying asleep*** (n=?/10) • **Index trauma from military service** • Mean BL PTSD severity (Global Impression of Severity*): 3.3 ± 0.9 • Allowed to continue stable medications and/or psychotherapy • Excluded if: + screen for "illicit" drugs including THC	7 weeks each *2-week washout*

Bonn-Miller et al 2021[4,13]
NCT02759185
Parallel, DB, PC, *pilot* RCT (in phase I) #
	• Adults (90% male) with **chronic, treatment-resistant PTSD** (n=80/76)
	• **Combat-related trauma (67.5%)**
	• Mean BL CAPS-5 total score *range* (by tx group): 36.6–38.0
	• Allowed to continue stable medications and/or psychotherapy
	• Cannabis use prohibited within 2 weeks of the trial
	  • **Moderate cannabis withdrawal scores for each tx group at BL**
	• Excluded if:
	  • personality disorder, primary psychotic disorder, bipolar type 1, serious suicidality, severe depression,
	  • + urine screen for for non-prescribed opiates, (meth)amphetamines, cocaine; or current SUD (except mild CUD)
		3 weeks
		
		(2-week washout before 3 weeks of tx in phase II)

* A global severity score of 4 = "extreme"

In phase II, participants crossed over to receive 1 of 3 cannabis treatments (no placebo); we focus on phase 1 results

Abbreviations: BL, baseline; CT, clinical trial; CUD, cannabis use disorder; DB, double-blinded; PC, placebo-controlled; PTSD, post-traumatic stress disorder; R(C)T, randomized controlled trial; SUD, substance use disorder; THC, (delta-9)-tetrahydrocannabinol; Tx, treatment;

OVERVIEW OF MULTI-DOSE SYMPTOMATIC TRIALS (APPROACH 1)

Trial and design	Population (total/completed n)	Approx. tx. length

Walsh et al 2023[5,14] NCT02517424 *Converted to* before-after, uncontrolled RT*	• Adults (83% male) with **chronic, treatment-resistant PTSD** (n=6/5)
	• BL total PCL-5 score ≥ 40
	• Allowed to continue stable medications and/or psychotherapy
	• No cannabis use for 8 weeks before trial
	• Excluded if:
	  • certain personality disorder, primary psychotic disorder, bipolar disorder, depression with psychosis, severe suicidality
	  • + urine screen for for non-prescribed opiates, (meth)amphetamines, cocaine; or current SUD including CUD
		3 weeks

NCT03248167[6] Parallel, DB, PC RCT *Limited results posted*	• Adults (36.7% male) with **moderate-to-severe AUD and PTSD or subPTSD** (n=30/21)
	• Mean (SD) BL total PCL-5 total score: CBD, 42.1 (13.9); PBO, 49.2 (13.8)
	• Excluded if:
	  • AUD treatment and/or recent psychotherapy start for any psychiatric condition
	  • Schizophrenia, schizoaffective disorder, bipolar type 1, serious suicidality, inpatient psychiatric treatment in prior 12 mo.
	  • + urine screen for opioid; moderate-to-severe non-alcohol SUD, CUD
		6 weeks

* Designed as a placebo-controlled parallel RCT, but due to under recruitment, investigators reported only within-participant changes from BL

SubPTSD = meeting PTSD DSM-5 criterion part A, F, G, and H, and having at least 6 symptoms from criterion B–E.

Abbreviations: AUD, alcohol use disorder; BL, baseline; CBD, cannabidiol; CUD, cannabis use disorder; DB, double-blind; mo., month; PC, placebo-controlled; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; R(C)T, randomized controlled trial; THC, (delta-9)-tetrahydrocannabinol; Tx, treatment

APPROACH 1 – SELECT EFFICACY RESULTS

<table>
<tr><th>Study</th><th>Intervention(s)</th><th colspan="5">Efficacy</th></tr>
<tr><td rowspan="4">Jetly 2015[3]</td><td rowspan="4">Nabilone 0.5–3 mg vs PBO, once nightly, titrated to response</td><td colspan="3" rowspan="2">Mean (SD) change from BL to week 7 in CAPS recurring/distressing dreams sub-score</td><td>Nabilone</td><td>PBO</td></tr>
<tr><td>–3.6 (2.4)</td><td>–1.0 (2.1)</td></tr>
<tr><td colspan="5">Favors nabilone (P=0.03)</td></tr>
<tr><td colspan="5">• No differences in changes in CAPS difficulty falling/staying asleep scores</td></tr>
<tr><td colspan="5">• Mean change in well-being scores favors nabilone to PBO (P=0.04)</td></tr>
<tr><td rowspan="4">Bonn-Miller 2021[4]</td><td rowspan="4">Smoked cannabis, ad libitum:
High THC:
THC 12%/CBD <0.05%;
Balanced THC/CBD:
THC 7.9%/CBD 8.1%;
High CBD:
THC0.5% /CBD 11%
vs PBO,
each up to 1.8 g/day</td><td rowspan="2">Mean (SD) change from BL to week 3 in total CAPS-5 score (primary)</td><td>High THC</td><td>Balanced</td><td>High CBD</td><td>PBO</td></tr>
<tr><td>–15.3 (11)</td><td>–8.5 (10)</td><td>–8.4 (10)</td><td>–13.1 (12)</td></tr>
<tr><td colspan="5">• Significant within-group changes, but CBPs not superior to PBO (P=0.15)</td></tr>
<tr><td colspan="5">• No differences between groups in change in PCL-5 score</td></tr>
<tr><td colspan="5">• Insomnia symptoms (on ISI) improved in each group, with no significant differences between treatment groups</td></tr>
</table>

Key: green/bold, efficacy favors CBP over comparator (statistically);
grey, efficacy favors neither CBP or comparator (statistically)

Abbreviations: BL, baseline; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; ISI, Insomnia Severity Index; PBO, placebo; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; THC, (delta-9)-tetrahydrocannabinol;

APPROACH 1 - SELECT EFFICACY RESULTS

Study	Intervention(s)	Efficacy				
Walsh 2023[5]	Vaporized cannabis, *ad libitum:* High THC: THC 10±2% , CBD <1%; Balanced THC/CBD: THC 10±2%, CBD 10±2% ; each up to 2 g/day	Mean (SD) CAPS-5 total score (primary)	**BL**		**Week 3**	
			39.0 (5.9)		30.7 (11.2)	
			• Numerical reduction in total symptoms, not statistically significant (P=0.11) • No comparator group			
NCT03-248167[6]	CBD 600 mg vs PBO daily	Mean (SD) PCL-5 total score (co-primary)	**BL**		**Week 6**	
			CBD	42.1 (13.9)	**CBD**	26.6 (18.5)
			PBO	49.2 (13.8)	**PBO**	26.9 (17.7)
			• Numerical symptom reductions in both groups; no statistical test reported • No differences in group scores at BL (P=0.1755) or week 6 (P=0.9119) per a simple t-test*			

Key: grey, efficacy favors neither CBP or comparator (statistically)

* Authors of this review performed two separate 2-sample t-tests (for BL and week 6) with equal variance as a preliminary assessment in the absence of reporting results of a statistical test by authors

Abbreviations: BL, baseline; CAPS-5, Clinician-Administered PTSD Scale for DSM-5 CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; PBO, placebo; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; SD, standard deviation; THC, (delta-9)-tetrahydrocannabinol;

OVERVIEW OF LABORATORY TRIALS ON THE ACUTE EFFECTS OF A SINGLE DOSE (APPROACH 2)

Trial and design	Population (total/completed n)	Tx

Bolsoni et al 2022[7]
Parallel, DB RCT
 	
Traumatic memory recall test
	• Adults (24.2% male) with PTSD (n=33/33)
	• Mean (SD) BL PCL-5 score: CBD: 52.5 (12.1); PBO: 54.1 (9.2)
	• Excluded if:
	  • history of drug abuse or dependence;
	  • psychiatric condition other than depression or anxiety
	• **Mood or anxiety disorder: CBD: 88.2%; PBO: 37.5%**
		Single dose
		Tests 90 min after drug adm.
		Follow-up 1 week after dose

NCT02069366[15] – parallel, DB, RCT, primarily focused on fMRI outcomes, with **3 published sub-trials**:		

Rabinak et al 2020[9]*
Threat processing task
	• Adults (26.3%-31.6% male in PTSD group) with PTSD (completed n=51-71 total/19-21 in PTSD group)
	• Mean (SD) CAPS-5: THC: 34.4 (11.2); PBO: 34.2 (6.4)
	• Excluded from PTSD group if:
	  • primary anxiety disorder, bipolar, schizophrenia, personality disorder, SI, MDD or alcohol/drug abuse or dependence in past 6 months
	  • use of SSRIs, current exposure-based PTSD therapy
	• ~30% of PTSD group with cannabis use in the past 30 days
		Single dose
		
		Tests 120 min after drug adm.

Pacitto et al 2022[10]* Emotion regulation task		
Zabik et al 2023[11]* Fear-extinction protocol		**Single dose, 3-days of tests** Drug. adm on day 2, 120 min before test

* Approximate characteristics due to slight differences between sub-trials (patients were excluded for poor data – eg, during fMRI) or poor reporting. Rabinak et al and Zabik et al included healthy controls and trauma-exposed controls, whereas Pacitto et al included only trauma-exposed controls.

Abbreviations: Adm., administration; CAPS-5, Clinician-Administered PTSD scale for DSM-5; DB, double-blinded; fMRI, functional magnetic resonance imaging; MDD, major depressive disorder; PBO, placebo; PCL-5, PTSD checklist for DSM-5; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; SD, standard deviation; SI, suicidal ideation; SSRI, selective serotonin reuptake inhibitor; Tx, treatment;

APPROACH 2 – SELECT RESULTS

Study	Tx(s)	*Select* behavioral and/or fMRI outcome(s)
Bolsoni 2022[7,8]	CBD 300 mg **vs** PBO	• **CBD improved cognitive impairment** vs PBO at 90 min, with significance 1-week later • CBD **reduced anxiety** vs PBO in the non-sexual trauma subgroup only, *in a post-hoc analysis*
		• No difference in sedation or discomfort scores
NCT02-069366[9-11]	Dronabinol (THC) 7.5 mg **vs** PBO	<u>THC vs PBO in PTSD group:</u> • **↓ amygdala and ↑mPFC/rACC activation** during a threat processing task • **↑ cerebellar activation** when viewing neutral images during an emotional regulation task • **↑ left amygdala activation** in response to an extinguished controlled stimulus during early fear renewal (part of an extinction learning protocol) on the day after study drugs were given
		Per investigators, <u>results preliminarily suggest/support:</u> • Potential role of THC in modifying the processing of threats by the corticolimbic system in people with PTSD • Investigation of THC as an adjunct to cognitive reappraisal therapy or exposure-based therapy

Key: green/bold, efficacy favors CBP over PBO (statistically); grey, efficacy favors neither CBP or PBO (statistically);

Abbreviations: CBD, cannabidiol; CBP, cannabis- or cannabinoid-based product; mPFC, medial prefrontal cortex; PBO, placebo; PTSD, post-traumatic stress disorder; rACC, rostral anterior cingulate cortex; THC, (delta-9)-tetrahydrocannabinol; tx, treatment;

OVERVIEW OF CBP AS AN ADJUNCT TO PE TRIALS (APPROACH 3)

Trial and design	Population (total/completed n)	Approx. tx. length

NCT05132699[12]
Parallel, DB, pilot, RCT
	• Adults (62% male) with PTSD (n=21/18)
	• BL mean CAPS-5 score: CBD: 42; PBO: 43
	• Receiving a stable non-interacting medication regimen
	• Excluded if:
	  • + urine screen for opiates, cocaine, methamphetamines, *or cannabis*
	  • Past-year history of drug abuse
	  • Severe alcohol abuse
	  • Psychosis, mania, or high suicide risk
		18 days
		
		CBD x 18 days started before PE; PE delivered over 14 days

Abbreviations: BL, baseline; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; CBD, cannabidiol; DB, double-blinded; PBO, placebo; PE, prolonged exposure; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; Tx, treatment;

APPROACH 3 – SELECT EFFICACY RESULTS

Study	Intervention(s)	Efficacy			
NCT05-132699[12]	CBD 250 mg **vs** PBO <u>twice daily</u>, as an *adjunct to massed PE*	Mean (SEM) **PCL-5 Total Score*** (primary outcome)			• Numerical symptom reductions in both groups • No statistical test reported by authors • No differences in group scores at BL (P=0.9062) or day 45 (P=0.6457) per a simple t-test[#]
		Time point	**CBD**	**PBO**	
		BL	50.8 (0.9)	52.1 (0.9)	
		Day 45 (1-month after tx end)	20.0 (7.6)	27.3 (8.1)	

Key: grey, efficacy favors neither CBP or comparator

*Similar results achieved using the CAPS-5 total score: numerical reductions in both groups, except results slightly favor PBO over CBD numerically (no differences per simple t-test)

[#] Authors of this review performed two separate 2-sample t-tests (for BL and day 45) with equal variance as a preliminary assessment in the absence of reporting results of a statistical test by authors

Abbreviations: BL, baseline; CAPS-5, Clinician-Administered PTSD scale for DSM-5; CBP, cannabis- or cannabinoid-based product; PBO, placebo; PCL-5 PTSD Checklist for DSM-5; PE, prolonged exposure therapy; PTSD, post-traumatic stress disorder; SEM, standard error of the mean; tx., treatment;

COMBINED SAFETY: SELECT RESULTS

- AE information for studied CBPs reported for 5 trials, some with limited details
  - Mostly mild to moderate severity AEs[3,4,6,12,15]
  - Not associated with worsened PTSD total symptom scores on average[4,5,6,12]
  - Discontinuation due to AEs
    - Bonn-Miller et al: n=13 (8.3%), overall, combined in phase I and phase II[4]
    - Jetly et al: 0%[3]

- Reported psychiatric AEs (apparently non-severe)
  - Suicidal ideation
    - Smoked cannabis: 4 total participants (3.6-5.9%, per tx group)[4]
    - Oral CBD 600 mg: 1 participant (5.9%)[6]
  - Other AEs reported by a CBP recipient in at least 1 trial (studied CBP):
    - Anxiety (smoked cannabis)[4]
    - Feeling overwhelmed (oral CBD)[6]
    - Lack of motivation (oral CBD)[6]
    - Emotional problems (oral CBD)[12]
  - Sleep-related AEs
    - *Increased* nightmares and insomnia: CBD (36.4%) vs PBO (0%), both given as an adjunct to PE[12]
    - Nightmares: CBD (5.9%) vs PBO (15.4%)[6]

Abbreviations: AE, adverse event; CBD, cannabidiol; CBPs, cannabinoid- or cannabis-based products; PE, prolonged exposure; PTSD, post-traumatic stress disorder;

ROB ASSESSMENT

- ROB by an SR[1,2] was available for **3 of 7 trials:**
  - Low overall risk: Bonn-Miller et al 2021[1]
  - **High overall risk: Jetly et al 2015[1]**
    - Insufficient reporting: randomization and allocation concealment, baseline characteristics
    - potential problems with cross-over analysis (lack of reporting for each period, inappropriate statistical analysis)
  - Unclear/some concerns: Rabinak et al 2020[2]
    - insufficient reporting about randomization, and allocation concealment

- Noted concerns (not comprehensive) for 4 trials without ROB assessment:
  - Insufficient detail to assess 2 trials that are only published on clinicaltrials.gov[6,12]
  - Insufficient details about randomization (N=1),[5] and concealment (N=2)[5,7]

- Other concerns: potential confounding bias
  - Cannabis-withdrawal symptoms (Bonn-Miller et al 2021)[4]
  - Numerically more participants with mood/anxiety disorder in CBD group (Bolsoni et al 2022)[7]
  - Exact utilization of concurrent medications and/or therapies in most multi-dose CBP trials unknown[3,4,5,6,12]

Abbreviations: CBD, cannabidiol; ROB, risk of bias; SR, systematic review;

SELECT LIMITATIONS

- Some trials with significant concerns for bias, including Jetly et al 2015
- Incomplete results available from some trials
- Lack of long-term *experimental data*
- Potential generalizability concerns, for example:
  - Jetly et al included participants per DSM-4-TR criteria, which may not be generalizable to all patients meeting DSM-5 criteria for PTSD[16]
  - Participant's characteristics may not be generalizable to all patients
    - *Jetly et al 2015:* men with chronic PTSD and sleep disturbances at baseline whose index traumatic event occurred during military service[3]
  - Many trials excluded participants with a current or historical SUD
  - Differences between medical cannabis products available to Utah patients and those studied in trials

Abbreviations: DSM-4/5, Diagnostic and Statistical Manual of Mental Disorders – Fourth or Fifth edition; PTSD, post-traumatic stress disorder; SUD, substance use disorder;

CONCLUSIONS FROM THE VA/DOD PTSD GUIDELINE (2023)

- Developed using a systematic literature search, with cited evidence including SRs of ECTs, observational studies, and/or case reports[17]

- **Strongly recommends against** CBPs for treatment of PTSD (very low quality of evidence), due to[17]:
  - Lack of good-quality RCT evidence demonstrating efficacy
  - Evidence of harms from non-RCT evidence, for example:
    - Emergent/worsened depression, anxiety, psychosis, substance misuse, suicidality, agitation, paranoia

Abbreviations: CBPs, cannabis- or cannabinoid-based product; DoD, Department of Defense; ECT, experimental controlled trials; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; SR, systematic review; VA, Department of Veteran's Affairs

CURRENT UTAH CRRB GUIDANCE FOR PTSD

Includes 1 formal (ie, graded) conclusion:

"There is insufficient evidence to support the conclusion that medical cannabis or cannabinoids are effective or ineffective for PTSD or symptoms of PTSD"[18]

- Similar conclusions to the 2023 VA/DoD guideline
- Due to uncertain efficacy and potential for harm, guidance suggests considering cannabis for people who fail or cannot tolerate evidence-based PTSD treatments, when the risks of severe PTSD outweigh the potential risks of cannabis therapy

Abbreviations: CRRB, (Utah) Cannabis Research Review Board; DOD, Department of Defense; PTSD, post-traumatic stress disorder; VA, Department of Veteran's Affairs

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR PTSD

- Graded statement about effectiveness for PTSD or PTSD symptoms
  - Consider including this statement unchanged (insufficient evidence)
    - Of 4 RCTs with applicable evidence, 1 lacks a comparator group,[5] 2 suggest that cannabis is not better than placebo,[4,6] and 1 trial considered to have a high ROB found nabilone significantly reduced nightmares compared to placebo[3]

- May consider adding a statement about cannabinoids or cannabis as an adjunct to psychotherapy for PTSD
  - Evidence of efficacy for this use could be considered insufficient

  - Additional evidence may become available soon:
    - Published results of NCT05132699 (included in this review based on partial results posted to clinicaltrials.gov)[12]
    - NCT03518801[19]
      - RCT of CBD as an adjunct to PE
      - Estimated completion September 30, 2024

Abbreviations: CBD, cannabidiol; CRRB, Utah Cannabis Research Review Board; LOE, level of evidence; PE, prolonged exposure; PTSD, post-traumatic stress disorder; RCT, randomized controlled trials; ROB, risk of bias

CONSIDERATIONS FOR UPDATES TO CRRB GUIDANCE FOR PTSD

- Additional considerations for <u>elaboration in guidance</u>:
  - Elaborate about the characteristics of available RCTs, particularly those published in a peer-reviewed journal, including:
    - study design, major clinical characteristics, types and routes of administration of cannabis or cannabinoids used, and major bias concerns or limitations (see report section 3 and 4)
  - Consider discussing/reviewing the current CRRB guidance about the best candidates for treatment of PTSD with medical cannabis (see last paragraph on page 7)
- Area of active research (see report section 8)
  - May wish to make note of potential future studies for review when they become available

Abbreviations: CBD, cannabidiol; CRRB, Utah Cannabis Research Review Board; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial;

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Extra slides

NATIONAL ACADEMIES LOE RATINGS*[20]

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).
"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).
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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[20]

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).
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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis.

Abbreviations: LOE, level of evidence;

NATIONAL ACADEMIES LOE RATINGS*[20]

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).
"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).

*LOE ratings for therapeutic effects from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis.

Abbreviations: LOE, level of evidence;

OVERVIEW OF STUDIED CANNABIS-RELATED TREATMENTS

Trial *Approx. tx length*	Studied Cannabinoid- or Cannabis-based Product (CBP)
Trials for Symptomatic Treatment of PTSD with Multiple CBP Doses	
Jetly et al 2015[3] *7 weeks*	(Oral*) nabilone 0.5 to 3 mg 1 hour before bedtime, titrated to suppression of nightmares over up to 5 weeks and then continued at that dose for 2 weeks. Mean dose: 1.95 ± 0.9 mg.
Bonn-Miller et al 2021[4] *3 weeks*	Smoked cannabis (high THC, balanced THC/CBD, or high CBD) administered *ad libitum* up to 37.8 grams over 3 weeks (1.8 grams/day), delivered using a metal pipe. • High THC: 12% THC, <0.05% CBD (mean 10.4 grams over 3 weeks) • Balanced THC/CBD: 7.9% THC, 8.1% CBD (mean 8.2 grams over 3 weeks) • High CBD: 0.5% THC, 11% CBD (mean 14.3 grams over 3 weeks)
Walsh et al 2023[5] *3 weeks*	Vaporized cannabis (high THC or balanced THC/CBD) administered *ad libitum* up to 2 grams/day using a portable cannabis vaporizer of unspecified type: • High THC: 10±2% THC, <1% CBD • Balanced THC/CBD: 10±2% THC, 10±2% CBD
NCT03248167[6] *6 weeks*	(Oral*) CBD 600 mg daily

*Route of administration not reported, but we infer that doses were administered orally.

Abbreviations: Approx., approximate; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; PTSD, post-traumatic stress disorder; THC, delta-9-tetrahydrocannabinol; Tx, treatment

OVERVIEW OF STUDIED CANNABIS-RELATED TREATMENTS

Trial *Approx. tx length*	Studied Cannabinoid- or Cannabis-based Product (CBP)
Single CBP Dose Trials in a Laboratory Setting	
Bolsoni et al 2022[7] *1 dose*	(Oral) CBD 300 mg dissolved in corn oil and packed in gelatin capsules, administered one time about 90 minutes before a behavioral test
NCT02069366[15] Rabinak 2020,[9] Pacitto 2022,[10] Zabik 2023[11] *1 dose*	(Oral) dronabinol 7.5 mg one time 120 minutes before an fMRI scan and tests
Multiple CBP Doses as an Adjunct to Massed Prolonged Exposure (PE) Therapy	
NCT05132699[12]	(Oral) CBD (as Epidiolex) 250 mg twice daily (in AM and evening after high fat meals), starting 3 days before the first day of PE

Abbreviations: Approx., approximate; CBD, cannabidiol; CBP, cannabinoid- or cannabis-based product; PE, prolonged exposure; PTSD, post-traumatic stress disorder; Tx, treatment