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Nabilone for the Treatment of Posttraumatic Stress Disorder: A 2023 Update

Rapid Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

PTSD	posttraumatic stress disorder
RCT	randomized controlled trial

Key Messages

- One relevant systematic review of high methodological quality did not include any randomized controlled trials (RCTs) on the effectiveness of nabilone for the treatment of posttraumatic stress disorder (PTSD).
- We did not find any evidence-based guidelines on the use of nabilone for adults with PTSD.

Context and Policy Issues

PTSD is a chronic psychiatric disorder that can develop in individuals who have experienced or witnessed a traumatic event or series of events, such as natural disasters, war or combat, motor vehicle accidents, or other exposures to actual or threatened death, serious injury, or sexual violence.[1,2] Common symptoms of PTSD include intrusive thoughts, nightmares, flashbacks, dissociation, feelings of sadness or guilt, and intense distress at real or symbolic reminders of the trauma.[3] People with PTSD can be at higher risk for other mental health conditions, including depression, substance use disorders, anxiety disorders, and sleep disorders.[1,4,5] PTSD and these common comorbidities are associated with decreased quality of life and function, disability, and increased mortality.[6-10]

Research suggests that approximately 9.2% of people in Canada will have PTSD at some point in their lives.[11] This rate is higher in women and in occupational groups who are at increased risk of experiencing traumatic events, such as health care workers, first responders, and correctional workers.[11-14]

Treatment strategies for managing PTSD include pharmacotherapy, psychotherapy (e.g., cognitive behavioural therapy), or other nonpharmacological interventions (e.g., exercise).[15] Selective serotonin reuptake inhibitors (e.g., paroxetine, fluoxetine, sertraline) and serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine) are often recommended as first-line pharmacological interventions for PTSD.[16] In recent years, there has been growing interest in studying the potential role of cannabinoids for the treatment of PTSD.[17-19] Cannabinoids are a class of biological compounds that bind to cannabinoid receptors, which are involved in multiple intracellular signal transduction pathways implicated in regulating various physiologic and cognitive processes.[20-22] Many cannabinoids are derived naturally from plants of the *Cannabis* genus, but they can also be synthetically produced.[23] Nabilone is a synthetic cannabinoid that is chemically similar to tetrahydrocannabinol, the primary psychoactive component of cannabis. Originally approved for treating chemotherapy-induced nausea and vomiting, it has been proposed as a possible therapeutic option for the management of PTSD due to its route of administration (i.e., oral) and pharmacokinetic properties.[24,25]

CADTH has previously reviewed literature regarding the use of nabilone for the treatment of adults with PTSD. A 2019 CADTH report[26] identified 2 relevant primary studies (1 crossover RCT and 1 retrospective chart review). Within the crossover RCT, participants experienced a reduction in the frequency of nightmares while being treated with nabilone compared to when they were receiving placebo.[26] Participants in the retrospective cohort study reported a statistically significant decrease in PTSD symptoms (including insomnia and nightmares) following treatment with nabilone compared with before treatment.[26] In 2021, CADTH conducted an update to the 2019 report,[27] in which 2 additional systematic reviews (that included a total of 1 relevant single-arm, open-label cohort study) were identified for inclusion.

Findings of the single-arm, open-label cohort study suggested that some patients (72% of the study population [34 of 47]) experienced total cessation or reduction of nightmares during treatment with nabilone.[27] Although these 3 primary studies suggested that treatment with nabilone may be associated with improvements in some PTSD symptoms, the available evidence was of limited quantity and had methodological limitations (e.g., lack of studies with active control groups, small sample sizes, limited generalizability to the overall PTSD population in Canada) that made it difficult to draw conclusions on the effectiveness of nabilone for the treatment of PTSD.[26,27] Additionally, neither of the previous CADTH reports[26,27] identified evidence-based guidelines that included recommendations regarding the use of nabilone for the treatment of PTSD.

The objective of the current report is to is to identify and summarize the clinical evidence and the evidence-based guidelines regarding the use of nabilone for the treatment of adults with PTSD published since the 2021 CADTH report[27] on this topic.

Research Questions

1. What is the clinical effectiveness of nabilone for the treatment of posttraumatic stress disorder (PTSD) in adults?
2. What are the evidence-based guidelines regarding the use of nabilone for the treatment of PTSD in adults?

Methods

Literature Search Methods

The literature search strategy used in this report is an update of one developed for a previous CADTH report, run on October 20, 2021.[27] For the current report, a limited literature search was conducted by an information specialist on key resources, including MEDLINE, Embase, PsycINFO, the Cochrane Database of Systematic Reviews, the International HTA Database, Canadian and major international health technology agencies, as well as a focused internet search. For the current report, database searches were rerun on January 11, 2023, to capture any English-language documents published or made available since the last completed search. No filters were applied to limit the retrieval by study type. The search of major health technology agencies was also updated to include documents published since October 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. Because this is an update to previous CADTH reports, articles were included if they were made available since the previous search dates and not included in the 2021 or 2019 CADTH reports.[26,27] The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Publications that did not meet the inclusion criteria but provided

information related to real-world evidence for nabilone for adults with PTSD were compiled to be included in an Appendix.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were included in the 2021 or 2019 CADTH reports[26,27] on this topic. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews or in the 2021 or 2019 CADTH reports[26,27] were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodologies were also excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by 1 reviewer using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[28] as a guide. Summary scores were not calculated for the included study; rather, the strengths and limitations of each included publication were described narratively.

Patient Engagement

CADTH has adopted the CADTH Framework for Patient Engagement in Health Technology Assessment,[29] which includes standards for patient involvement in individual health technology assessments and is used to support and guide CADTH activities involving patients. For this report, CADTH engaged a patient contributor with lived experience of treating PTSD with nabilone.

Invitation to Participate and Consent

CADTH reached out to the PTSD Association of Canada and the Mental Health Commission of Canada. Both organizations have communities of people with lived experience of mental health conditions, including PTSD. A CADTH Patient Engagement Officer contacted the groups by email to explore their interest in becoming involved. The preliminary request included an overview of this project, the purpose of engagement, and the nature of

Table 1: Selection Criteria

Criteria	Description
Population	Adults with a diagnosis of PTSD
Intervention	Nabilone
Comparator	Q1: Active treatments (e.g., pharmacotherapy, psychotherapy); placebo; no treatment Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., severity of PTSD symptoms, anxiety, depression, quality of life, safety [e.g., adverse events, potential for misuse]) Q2: Recommendations regarding best practices (e.g., appropriate patient populations, recommended treatment protocols)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

PTSD = posttraumatic stress disorder; Q = question.

engagement activities. An individual was identified, and the Patient Engagement Officer obtained the person's informed consent to share their lived experiences with PTSD and nabilone with CADTH staff.

Engagement Activities

One contributor shared their personal experiences by video call during the drafting of the report. The patient's perspectives gained through engagement processes were used to ensure the relevance of the outcomes of interest for the clinical assessment and to provide insights, background, and context to help inform the Discussion section.

The patient's involvement was guided by the Guidance for Reporting Involvement of Patients and the Public (version 2) Short Form reporting checklist, which is outlined in Appendix 4.[30]

Summary of Evidence

Quantity of Research Available

A total of 38 citations were identified in the literature search. Following screening of titles and abstracts, 30 citations were excluded and 8 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 11 publications were excluded for various reasons, and 1 systematic review met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA[31] flow chart of the study selection.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 5. No publications that provided information related to real-world evidence for nabilone for adults with PTSD were identified.

Summary of Study Characteristics

One systematic review[32] met the selection criteria and was identified for inclusion in this review. No relevant health technology assessments, RCTs, nonrandomized studies, or evidence-based guidelines were identified.

The included systematic review[32] had broader inclusion criteria than the present review. Specifically, the authors evaluated the clinical effectiveness of any pharmacologic or nonpharmacologic interventions for PTSD or comorbid PTSD and substance use disorder in adults, including cannabinoids. The systematic review[32] was conducted as an update to 2 previous systematic reviews,[33,34] and informed updates to the PTSD Trials Standardized Data Repository (a comprehensive database of PTSD trials) by the National Center for PTSD. The systematic review[32] included RCTs published between June 1, 2018, and July 30, 2021 (studies published between 1980 and 2018 were eligible for the first review[34] in this series of systematic reviews). In total, 437 RCTs were included in the review (48 identified in the update); however, none of the included RCTs evaluated the clinical effectiveness of nabilone.

Additional details regarding the characteristics of the included systematic review[32] are provided in Appendix 2.

Summary of Critical Appraisal

The systematic review[32] had clearly defined research questions and study eligibility criteria that included components of population, intervention, comparator, outcomes, and time frame for follow-up. The review methods were established before conducting the review and were made available in a published protocol. No deviations from the protocol were identified, increasing the validity of the review.[32] The authors performed literature searches using multiple databases, described the search strategies in detail, including search terms and search restrictions (e.g., restrictions on publication date and language), presented a flow chart illustrating the study selection process, and provided a list of studies excluded after full-text review. These methodological strengths increase the transparency and reproducibility of the literature searches and article selection process. Article selection and data extraction were performed using at least 2 reviewers, decreasing the likelihood for inconsistencies in these processes. The review authors stated that they had no conflicts of interest related to this review and disclosed their source of funding, which was considered unlikely to have influenced the findings of the review.[32]

While the systematic review[32] was considered to be of high methodological quality, some limitations were identified. Specifically, the review[32] did not incorporate searches for grey literature and did not justify the decision to restrict study inclusion to articles published in English. As a result, there is a risk that relevant studies published outside of traditional publishing and distribution channels or in other languages were not captured.

The included systematic review[32] included no primary studies relevant to the current report. Consequently, additional critical appraisal considerations outlined in the AMSTAR 2,[28] such as the appropriateness of methods used for evidence synthesis and data analysis, were not assessed because they do not affect the interpretation of the evidence made in this report.

Additional details regarding the strengths and limitations of the systematic review[32] are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Nabilone for PTSD

No relevant evidence regarding the clinical effectiveness of nabilone for the treatment of PTSD in adults was identified; therefore, no summary can be provided.

Guidelines Regarding the Use of Nabilone for PTSD

No relevant evidence-based guidelines regarding the use of treat-and-release protocols for patients requiring emergency medical services were identified; therefore, no summary can be provided.

Limitations

Based on the findings of this report, there is a paucity of literature on the clinical effectiveness of nabilone for PTSD published since the 2021 CADTH review[27] on this topic. In addition, the current report and the 2 previous CADTH reviews[26,27] did not identify any evidence-based guidelines that provided recommendations on the use of nabilone in adults with PTSD.

Conclusions and Implications for Decision- or Policy-Making

One systematic review[32] on pharmacologic and nonpharmacologic treatments for PTSD was included in this review. However, the review[32] did not include any studies that examined nabilone. No evidence-based guidelines regarding the use of nabilone in patients with PTSD were identified.

Although the current report did not identify any studies that addressed the clinical effectiveness of nabilone for the treatment of adults with PTSD, previous CADTH reviews[26,27] have identified and summarized evidence from 3 primary studies. These comprised 1 crossover RCT and 2 single-arm cohort studies. As summarized in the 2019 CADTH review,[26] participants of the crossover RCT reported a reduction in the frequency of nightmares when treated with nabilone compared to when receiving placebo.[26] Findings from the 2014 retrospective, single-arm, cohort study indicated that participants experienced a statistically significant decrease in PTSD symptomology (including insomnia and nightmares) during treatment with nabilone compared with before treatment.[26] Regarding the 2009 single-arm, open-label, cohort study (which was described in the 2021 CADTH review),[27] the authors suggested that some patients (72% of the study population [34 of 47]) experienced total cessation or reduction of nightmares during treatment with nabilone.[27] In total, these 3 primary studies analyzed data from 161 participants.[26,27] The findings from these studies should be interpreted with caution because the available evidence was of limited quantity and had methodological limitations (e.g., lack of studies with active control groups, small sample sizes, limited generalizability to the overall PTSD population in Canada).[26,27]

After speaking with an individual with lived experience with nabilone as a treatment for PTSD, the outcomes that were identified as important to patients included anger, aggression, anxiety, and sleep quality. Although the primary studies summarized in the previous CADTH reports evaluated the potential impact that nabilone could have on sleep-related outcomes, there appears to be little published literature on the effects of nabilone on anger, aggression, and anxiety in adults with PTSD.

Future higher-quality research examining the clinical effectiveness of nabilone for the treatment of adults with PTSD is warranted before conclusions on the potential role of nabilone can be drawn. Investigators of future trials may want to consider using outcome measures identified as important by the patient contributor involved in this review or outcome measures that do not appear to be represented in the currently available evidence (e.g., quality of life, potential for misuse). Additional studies evaluating the effects of nabilone for PTSD may encourage the development of evidence-based guidelines, which would be useful tools to inform clinicians and policy-makers involved in providing care for adults with PTSD.

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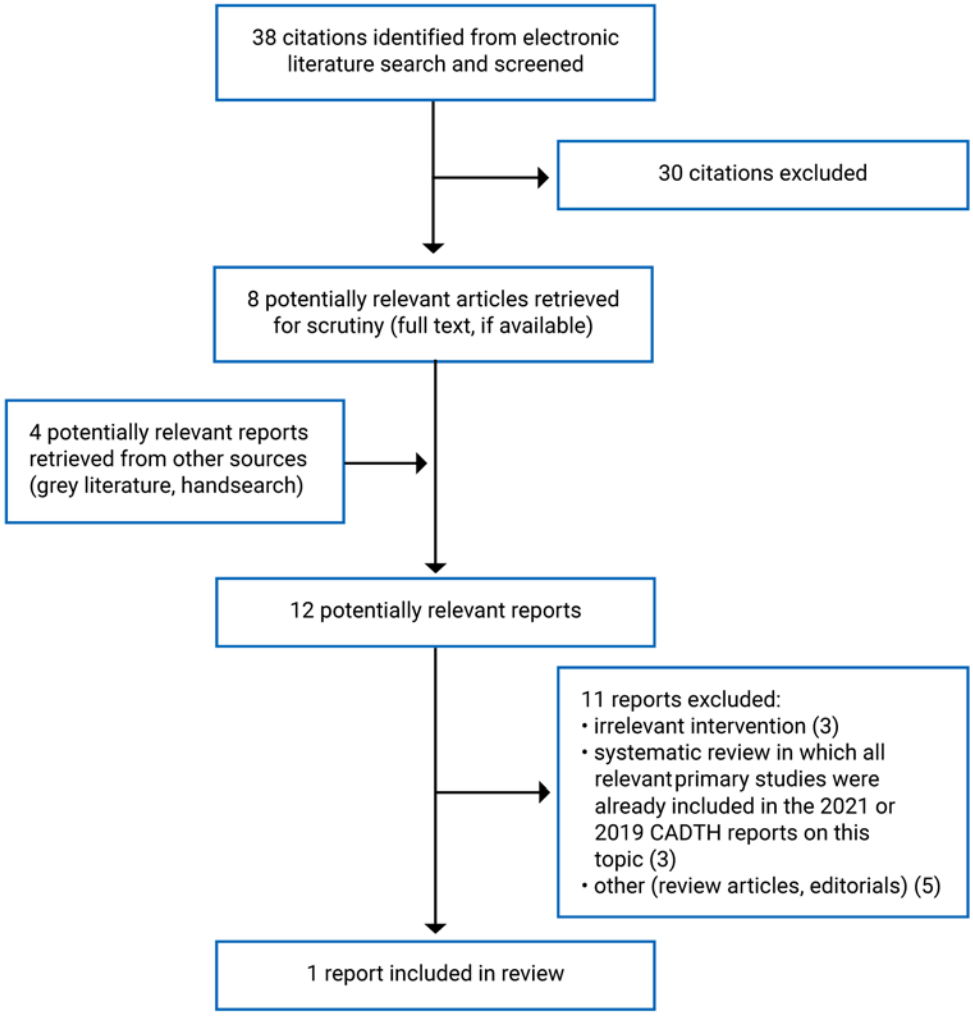
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study design and number of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
O'Neil et al. (2022)[32] US **Funding source:** Agency for Health care Research and Quality.	**Study design**: Systematic review of RCTs. The report was an update to 2 previous systematic reviews.[33,34] **Number of included studies**: In total, 437 RCTs were included in the systematic review. None of the included RCTs were relevant to the current report.	Studies of adults (mean age ≥ 18 years old) diagnosed with PTSD by a clinician or through a patient-reported assessment tool were eligible for inclusion.	**Intervention:** Any pharmacological and nonpharmacologic treatments for PTSD, comorbid PTSD and SUD, or insomnia and nightmares related to PTSD. Only studies that examined nabilone were considered relevant to the current report. **Comparator**: Any comparator, such as alternative PTSD interventions, waitlist, minimal attention, usual care, or placebo.	**Clinical outcomes:** • PTSD symptom severity (e.g., PCL or CAPS scores) • PTSD diagnostic change • PTSD clinically meaningful change • Anxiety • Anger • Depression • Function • Quality of life • Sleep • Substance use • Suicide- and self-directed violence • Withdrawal due to adverse events • Serious adverse events **Follow-up**: Any length of follow-up was eligible.

CAPS = Clinician-Administered PTSD Scale; PCL = PTSD Checklist; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SUD = substance use disorder.

Appendix 3: Critical Appraisal of Included Publications

Note this appendix has not been copy-edited.

Table 3: Strengths and Limitations of the Systematic Review Using AMSTAR 2[28]

Strengths	Limitations
O'Neil et al. (2022)[32]	
• The research questions and inclusion criteria were clearly stated and included components of population, intervention, comparator, outcomes, and time frame for follow-up • The review methods were established before conducting the review (a protocol was posted on the AHRQ website) and were followed throughout the review process • The choice of included study designs (i.e., RCTs) was explained • Multiple databases were searched (i.e., PTSDpubs, Ovid MEDLINE, CENTRAL, Embase, CINAHL, SCOPUS, and PsycINFO). Additionally, reference lists of retrieved systematic reviews were examined for potentially relevant studies. • Detailed literature search strategies and search restrictions were provided (e.g., studies published in languages other than English were excluded) • A flow chart of study selection was provided • A list of studies excluded after full-text review, along with reasons for exclusion, was provided • Article selection was conducted by 2 independent reviewers (disagreements were resolved by consensus of the team of investigators) • All extracted data were dual reviewed for accuracy and completeness • The review authors described the included primary studies in adequate detail • The risk of bias of included primary studies was assessed using a satisfactory technique (i.e., Cochrane's RoB 2 tool) • The sources of funding for the included primary studies were provided • Review authors stated that they had no conflicts of interest related to this review • Sources of funding were disclosed (the report was conducted under contract to the AHRQ) and were unlikely to have had an effect on the findings of the review	• A grey literature search was not completed • The review authors provided no justification for limiting study inclusion to articles published in English

AHRQ = Agency for Healthcare Research and Quality; AMSTAR 2 = A Measurement Tool to Assess systematic Reviews 2; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; RCT = randomized controlled trial; RoB 2 = Risk of Bias 2.

Appendix 4: Guidance for Reporting Involvement of Patients and the Public (Version 2) Short Form Reporting Checklist

Note this appendix has not been copy-edited.

Table 4: Patient Involvement in Nabilone for the Treatment of Posttraumatic Stress Disorder

Section and topic	Item	Reported in section
Aim	The patient contributor was involved in sharing their experiences and perspectives of nabilone as a treatment for PTSD. The purpose of the engagement was to offer a different perspective of the treatment to allow for a more nuanced understanding of the literature and to identify gaps.	Methods
Methods	After giving informed consent, the patient contributor discussed their experiences of PTSD and of treatment with nabilone by video call with the Patient Engagement Officer and Research Officer.	Methods
Results of engagement	The researchers were made aware of the importance of several outcomes and themes. In particular, the relevance of the research question for patients and the outcomes that mattered (such as anger, aggression, anxiety, and sleep quality) were confirmed. They also commented on the efficacy of the same dose over a long duration, identifying the lack of tolerance development. One factor to consider is the transition period when initiating treatment with nabilone. Some patients who use cannabis within their treatment regimen report not initially liking nabilone.	Conclusions and Implications for Decision- or Policy-Making
Discussion and conclusions	Success of patient involvement in this report is related to several factors. First, the patient contributor was briefed on the objectives of the project and supported in their role. The research team was receptive to this involvement and used it in their approach to the clinical evidence. Established processes are in place, and compensation was offered for their time to participate in the project.	Conclusions and Implications for Decision- or Policy-Making
Reflections/critical perspective	The patient contributor was highly engaged in the conversation with CADTH staff. They reported the most distressing symptoms of PTSD that nabilone addresses, benefits to the medication, their experiences of taking the medication for a significant length of time, and their overall impressions and recommendations for the medication. Limitations to our approach include the sensitivity of discussing experiences with PTSD and the risk of triggering negative emotions during or after our engagement. This risk was mitigated by ensuring the patient was aware that they could stop the conversation at any point. They were also made given a crisis telephone number they could call should they require support after our call. Another limitation of our approach is that people need reliable access to phone and internet to contribute to CADTH, which may exclude some voices.	Conclusions and Implications for Decision- or Policy-Making

PTSD = posttraumatic stress disorder.

Appendix 5: References of Potential Interest

Real-World Evidence

No literature identified.

Systematic Reviews

Protocols

Liu JJW, Nazarov A, Easterbrook B, et al. Four decades of military posttraumatic stress: protocol for a meta-analysis and systematic review of treatment approaches and efficacy. *JMIR Res Protoc.* 2021;10(10):e33151. PubMed

Review Articles

Legare CA, Raup-Konsavage WM, Vrana KE. Therapeutic potential of cannabis, cannabidiol, and cannabinoid-based pharmaceuticals. *Pharmacology*. 2022;107(3-4):131-149. PubMed

Scherma M, Muntoni AL, Riedel G, Fratta W, Fadda P. Cannabinoids and their therapeutic applications in mental disorders. *Dialogues Clin Neurosci*. 2020 09;22(3):271-279. PubMed

Stack SK, Wheate NJ, Schubert EA. Medicinal cannabis for the treatment of anxiety disorders: a narrative review. *Curr Treat Options Psychiatry.* 2022;9(3):163-173.