



TITLE: Medical Marijuana for Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness and Guidelines

DATE: 11 January 2017

CONTEXT AND POLICY ISSUES

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that can occur after experiencing a traumatic, shocking or scary event, such as injury, violence, or death.¹⁻³ People with PTSD tend to experience traumatic nightmares and other sleep difficulties, as well as recurrent intrusive memories (e.g, flashbacks), exaggerated startle responses, negative changes in mood and cognition, and other debilitating symptoms.¹ Significant distress, along with social, occupational, and other functional impairment can result.¹ The lifetime prevalence of PTSD in Canada is estimated at 9.2%.^{2,3}

Marijuana, also referred to as cannabis, is used medically as an antiemetic, sedative, analgesic, and appetite stimulant.^{2,4} Marijuana contains hundreds of cannabinoid compounds. The two primary cannabinoids are delta-9-tetrahydrocannabinol (THC), which is responsible for producing the 'high' experienced by users, and cannabidiol, which is responsible for many of the pharmacological reactions but does not produce a high.⁴ Synthetic cannabinoids, such as nabilone, are also available. Unlike smoked marijuana, synthetic cannabinoids can be delivered via a standardized, reproducible dose.⁴

While marijuana is not currently an approved therapeutic product in Canada, the Health Canada website lists PTSD among many conditions in which medical marijuana may be considered of potential therapeutic benefit.^{5,6} Canadian health care practitioners can authorize their patients to access cannabis for medical purposes subject to certain terms and conditions.⁷ Nabilone is approved for use in Canada for the treatment of severe nausea and vomiting associated with chemotherapy in adults over the age of 18 years.²

In 2012, CADTH reviewed the clinical effectiveness and guidelines regarding the use of cannabinoids for the treatment PTSD, updating a 2009 Rapid Response published on the same topic.^{3,8} One uncontrolled open-label study evaluating nabilone was identified in 2009, and the updated literature search in 2012 did not identify any new evidence. While the study authors concluded that nabilone was effective in reducing some symptoms of PTSD, the 2009 CADTH

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report concluded that the evidence regarding the clinical effectiveness of cannabinoids for the treatment of PTSD was limited.

In 2015, CADTH reviewed the evidence of efficacy and safety of long-term nabilone (a synthetic cannabinoid) use in adult populations with PTSD and other chronic conditions.² One RCT conducted in the PTSD population was identified, and the study authors concluded that the results supported the use of nabilone for PTSD-related nightmares, but that replication was needed in larger patient groups. The CADTH report observed that evidence of safety and efficacy beyond nine weeks was lacking.

A 2013 CADTH report was unable to identify any relevant evidence-based guidelines regarding the use of medical marijuana for any specific medical conditions.⁹

The purpose of this Rapid Response report is to summarize the evidence of clinical efficacy for medical marijuana and synthetic cannabinoids in adult populations with PTSD, and identify any evidence-based guidelines for this population.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of medical marijuana for the treatment of post-traumatic stress disorder (PTSD) in adults?
2. What is the clinical effectiveness of synthetic cannabinoids for the treatment of PTSD in adults?
3. What are the evidence-based guidelines regarding the use of medical marijuana or synthetic cannabinoids in adult patients with PTSD?

KEY FINDINGS

Based on one systematic review (SR) which included six studies in adults with PTSD, there is evidence from very low-quality studies to support the efficacy of smoked marijuana, oral THC, and nabilone in reducing some symptoms of PTSD. Side effects, described as mild to moderate were reported for only one retrospective chart review, in which nabilone was discontinued in 28% of patients. There were no guidelines identified regarding the use of medical marijuana or cannabinoids in PTSD.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2011 and December 6, 2016.

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. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults with PTSD <i>Subgroup of interest: treatment-resistant patients</i>
Intervention	Q1 and 3: Medical marijuana or medicinal cannabinoids (e.g., THC, cannabidiol) alone or in combination with other treatment Q2 and 3: Synthetic cannabinoids (e.g., nabilone) alone or in combination with other treatment
Comparator	Q1 and 2: Any active comparator (e.g., psychotherapy [antidepressants, anticonvulsants, sedatives, beta-blockers], psychotherapy [e.g., trauma-focused cognitive behavioral therapy, eye movement desensitization and reprocessing], combination treatment); No treatment; Placebo; No comparator (for safety) Q3: No comparator
Outcomes	Q1 and 2: Clinical effectiveness (e.g., clinical benefit [anxiety relief, improvement in global symptom severity, improved sleep quality, improvements in measures of alcohol and drug utilization], symptom reduction [e.g., nightmares, stress, violent behavior, hyperarousal, negative affect], quality of life) Safety (e.g., tolerability, dependence and addiction, withdrawal, psychosis, behavioral changes, memory deficits, cognitive impairments, sedation) Q3: Evidence-based guideline recommendations regarding the use of the interventions of interest in the adult population with PTSD
Study Design	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), non-RCTs, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Articles were also excluded if they were captured in a systematic review or meta-analysis selected for inclusion in this Rapid Response. Finally, articles were excluded if the intervention was not prescribed or administered by the study investigators or other health care professionals (i.e., non-medical marijuana).

Critical Appraisal of Individual Studies

The included systematic review was critically appraised using the AMSTAR tool.¹⁰ A summary score was not calculated; rather, a review of the strengths and limitations of the systematic review was described narratively.

SUMMARY OF EVIDENCE

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Quantity of Research Available

A total of 206 citations were identified in the literature search. Following screening of titles and abstracts, 197 citations were excluded and nine potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these 13 potentially relevant articles, 12 publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

One systematic review met the inclusion criteria for this Rapid Response.¹¹ No additional randomized controlled trials (RCTs) or non-randomized studies not already included in the systematic reviews met the inclusion criteria for the review (Table A1, Appendix 2).

Country of Origin

The systematic review was performed by authors from the United States¹¹ (Table A1, Appendix 2).

Patient Population

The systematic review searched for studies published between January 1980 and March 2015 and included 13 studies, six of which evaluated either oral THC, nabilone, or smoked marijuana in the PTSD population, with sample sizes ranging from 10 to 104 participants.¹¹ The included studies were published between 2009 and 2015. The seven remaining studies evaluated oral THC in Tourette's Syndrome and for agitation in the Alzheimer's population (these populations are out of scope and therefore results are not reported in this review). Of the six included PTSD studies, one included patients (n = 104) at a mental health and correctional facility that treated adult male offenders with serious mental illness. Approximately 90% of these patients were diagnosed with PTSD, and many had varying comorbid diagnoses, including mood, psychotic and substance use disorders. Three of the studies included a total of 119 soldiers, combat veterans, or military personnel. In the remaining two studies (n = 57 participants), the nature of the PTSD was not provided (Table A1, Appendix 2).

Interventions and Comparators

Of the six studies in the PTSD population, three studies administered nabilone and the dose ranged from 0.5 mg to 6 mg per day (n = 2 studies), and from 0.5 mg to 3 mg (n = 1 study).¹¹ One of these studies compared nabilone with placebo, while the other two studies were retrospective chart reviews and did not have a control group. Two prospective studies administered smoked marijuana (no control group), one of which the dosage was described as ad lib, with approximately 23% THC and less than 1% cannabidiol. In the other smoked marijuana study, participants smoked approximately 2 g to 3 g per day. One study administered oral THC (no control group), range 0.5 mg to 5 mg per day. In at least three studies, the

intervention was administered as an add-on to other pharmacologic treatment. Details regarding these treatments were not provided, although for two studies the medications were described as psychotropic (Table A1, Appendix 2).

Outcomes

The systematic review evaluated the strength of the evidence for the efficacy of marijuana and other cannabinoids on the symptoms of PTSD.¹¹ The included studies reported on nightmare quantity and intensity, sleep quality and quantity, daytime flashbacks, night sweats, quality of life, and pain. Limited information was provided on adverse events for the included studies. Outcomes were generally assessed through the administration of questionnaires such as the Clinician Administered PTSD Scale (CAPS), which evaluates PTSD symptoms (Table A1, Appendix 2).

Summary of Critical Appraisal

Based on the AMSTAR assessment, the systematic review appeared to be satisfactory. The narrative summary appeared to be an appropriate approach given the differences in the study populations of the identified studies (e.g., patients with comorbid mental health conditions), the variations in study design (one RCT, two retrospective chart reviews, and three prospective observational studies, often with limited data provided), and variations in the form and dosage of the intervention. The scientific quality of the included studies was thoroughly assessed and documented, and used appropriately in forming conclusions, with two authors independently rating the studies on quality, consistency, generalizability, and effect size using GRADE methodology. Only one database was searched, although this limitation was mitigated to some extent in that the authors attempted to identify other studies and conference abstracts using cross-referencing. It was not clear whether two investigators had selected studies and extracted data. The inclusion and exclusion criteria were not stated, and very limited details regarding the characteristics of the included studies were provided (Table A2, Appendix 3).

Summary of Findings

1. *What is the clinical effectiveness of medical marijuana for the treatment of post-traumatic stress disorder in adults?*

The systematic review¹¹ included two studies in which smoked marijuana was the intervention, and one study evaluating oral THC. All three studies reported improvement in the CAPS total score or subscores, two of which reported significant improvement (the third was a conference abstract that did not provide a statistical analysis). One study also reported a significant improvement in sleep quality, frequency of nightmares, and the *Clinical Global Impressions* scale. The conference abstract that did not include a statistical analysis also reported an improvement in quality of life and pain scores, as well as a discontinuation or lowering of dosage for sedatives and painkillers. While the findings suggested that smoked marijuana and oral THC are efficacious in treating some symptoms of PTSD, the authors cautioned that the overall GRADE of evidence was very low. Based on these findings and an evaluation of the quality of evidence, the authors concluded that there is very low-quality evidence to support the efficacy of using oral THC or smoked marijuana in treating nightmares and symptom severity in adults with PTSD and suggested caution in using medical marijuana for these disorders (Table A3, Appendix 4).

2. *What is the clinical effectiveness of synthetic cannabinoids for the treatment of post-traumatic stress disorder in adults?*

The systematic review¹¹ included three studies evaluating nabilone. One cross-over RCT evaluated 10 patients over 16 weeks, and reported significant improvement in nightmares, the *Clinical Global Impressions* score, and well-being as measured by the *General Well-Being Questionnaire*. One of two retrospective chart reviews reported a significant decrease in nightmares, a significant increase in hours of sleep, and in *Global Assessment of Functioning* scores. In the remaining retrospective chart review, 72% of participants reported a cessation of nightmares or reduction in nightmare intensity, a subjective improvement in sleep time and quality, and a reduction in daytime flashbacks and night sweats. In this study, nabilone was discontinued in 28% of patients due to side effects. Side effects were described as mild to moderate and included lightheadedness, forgetfulness, dizziness and headache. While the findings suggested that nabilone is efficacious in treating some symptoms of PTSD, the authors cautioned that the overall GRADE of evidence is very low. (Table A3, Appendix 4).

3. *What are the evidence-based guidelines regarding the use of medical marijuana or synthetic cannabinoids in adult patients with post-traumatic stress disorder?*

No guidelines regarding the use of medical marijuana or synthetic cannabinoids in adult patients with PTSD were identified.

Limitations

While all of the studies included in the systematic review reported improvement across a number of outcomes, the authors caution that the quality of the evidence is very low based on a detailed GRADE assessment. Of the six included studies, only one was an RCT, and it followed 10 patients for 16 weeks (crossover design, seven weeks for either the intervention or placebo, with a two-week washout). Two of the included studies were unpublished with limited information provided, and statistical analysis was not available. One of the studies included participants from a mental health and correctional facility that treated adult male offenders with serious mental illness. While 90% of these patients were diagnosed with PTSD, the study included patients with varying comorbid diagnoses, and 91% met criteria for marijuana dependence. Hence the results of this study may not be generalizable to the broader PTSD population. Three of the included studies were conducted in soldiers, veterans, or other military personnel, again impacting the generalizability of the findings to the broader PTSD population. For two of the included studies the nature of the trauma for the study participants was not stated. In at least three studies, the intervention was administered as an adjunct to other pharmacologic treatment (in two cases described as psychotropic), and hence it is difficult to evaluate the effect of the marijuana intervention specifically. Of the six included studies, side effects were reported for one study. The authors noted many factors that contribute to the low grade of evidence for the selected outcomes, including non-standardized administration of the intervention, concomitant use of other medications, lack of blinding or control groups, selective or incomplete reporting, inadequate or unreported statistical analysis, and poor generalizability.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on one systematic review, there is evidence from very low-quality studies that smoked marijuana, oral THC, and nabilone are efficacious in treating some symptoms of PTSD, particularly nightmares and sleep quality and quantity. Information regarding adverse events was reported for one observational study included in the systematic review, in which nabilone was discontinued in 28% of participants due to side effects described as mild to moderate (lightheadedness, forgetfulness, dizziness, and headache).³ Side effects of marijuana and cannabinoids commonly reported in the literature are generally rated as fairly mild, such as dizziness, tiredness, sedation, lightheadedness, headache, anxiety, disorientation, intoxication, nausea, and oromucosal discomfort.^{11,12} More serious reported side effects have been reported, such as seizures, hallucinations, and paranoid reactions.^{11,12} Tolerance, dependence, pulmonary effects, cognitive deficits, and driving impairment are also potential issues.^{11,12}

At least two RCTs are currently planned or underway to evaluate smoked or vapourized marijuana.^{13,14} The first will evaluate the safety and efficacy of three different potencies of vaporized marijuana in 42 participants with chronic, treatment-resistant PTSD, and is expected to be completed in April 2018.¹³ The other will evaluate the safety and efficacy of four different potencies of smoked marijuana in 76 veterans with chronic, treatment-resistant PTSD.¹⁴ Results are expected in October 2018.

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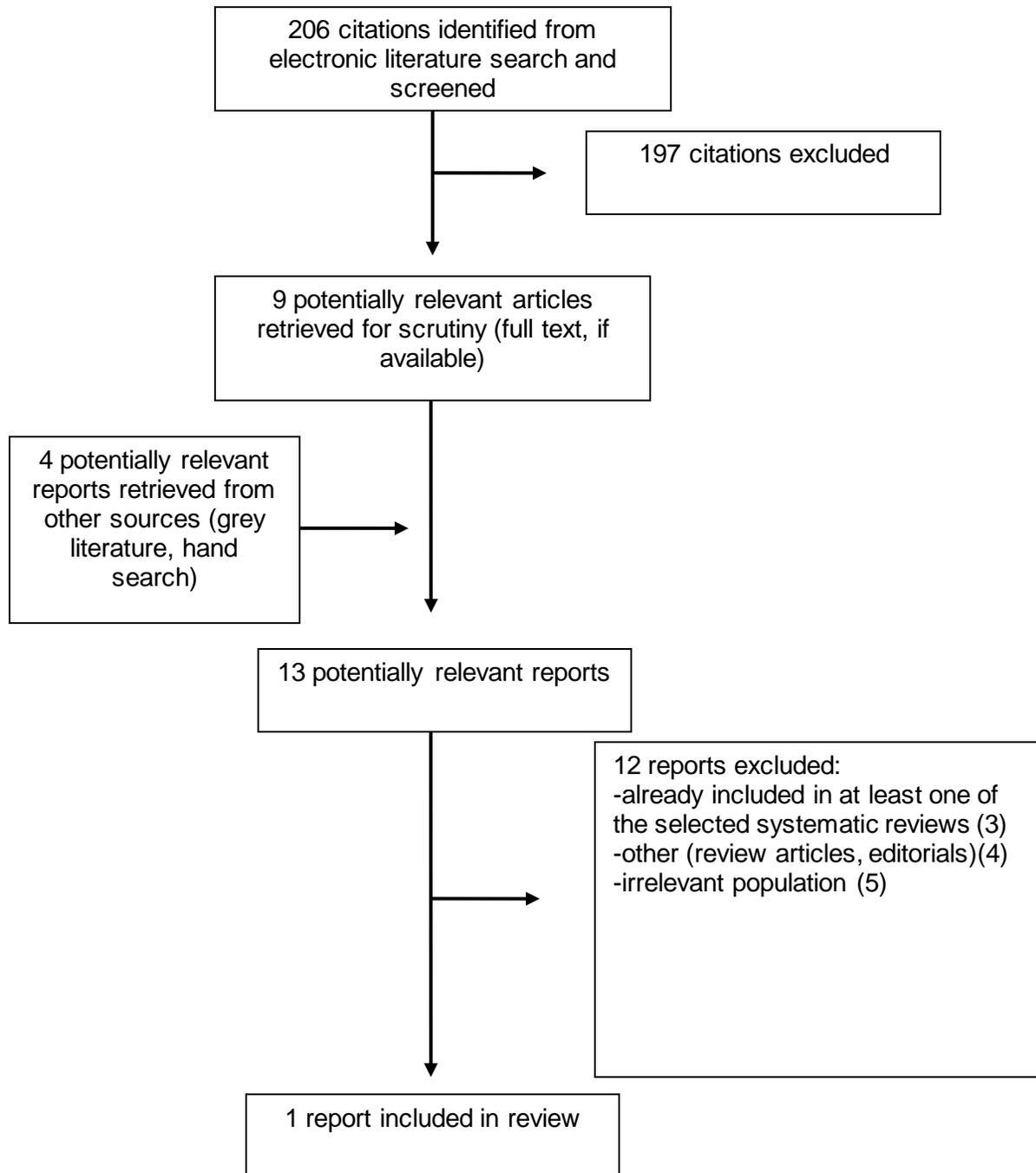
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REFERENCES

1. Mizrahi Zer-Aviv T, Segev A, Akirav I. Cannabinoids and post-traumatic stress disorder: clinical and preclinical evidence for treatment and prevention. *Behav Pharmacol*. 2016 Oct;27(7):561-9.
2. Long-term nabilone use: a review of the clinical effectiveness and safety [Internet]. Ottawa: CADTH; 2015 [cited 2016 Dec 12]. (Rapid response report: summary with critical appraisal). Available from: <https://www.cadth.ca/sites/default/files/pdf/htis/oct-2015/RC0715%20Long-term%20Nabilone%20Use%20Final.pdf>
3. Cannabinoids for the treatment of post-traumatic stress disorder: a review of the clinical effectiveness and guidelines [Internet]. Ottawa: CADTH; 2009 [cited 2016 Dec 12]. Available from: https://www.cadth.ca/media/pdf/L0144_Cannabinoids_for_PTSD_final.pdf
4. Clearing the smoke on cannabis: medical use of cannabis and cannabinoids - an update [Internet]. Ottawa: Canadian Centre for Substance Abuse; 2016 [cited 2016 Dec 12]. Available from: <http://www.ccsa.ca/Resource%20Library/CCSA-Medical-Use-of-Cannabis-Report-2016-en.pdf>
5. Consumer information - cannabis (marihuana, marijuana) [Internet]. Ottawa: Health Canada; 2016 [cited 2016 Dec 12]. Available from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/cons-eng.php>
6. Information for health care professionals. Cannabis (marihuana, marijuana) and the cannabinoids [Internet]. Ottawa: Health Canada; 2013 Feb. 4.0 Potential therapeutic uses. [cited 2017 Jan 3]. Available from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php#chp40>
7. Statement from Health Canada concerning access to cannabis for medical purposes [Internet]. Ottawa: Health Canada; 2016 Aug 11 [cited 2017 Jan 10]. Available from: <http://news.gc.ca/web/article-en.do?nid=1110389>
8. Cannabinoids for the treatment of post-traumatic stress disorder: a review of the clinical effectiveness and guidelines [Internet]. Ottawa: CADTH; 2012 [cited 2016 Dec 12]. (Rapid response report: summary with critical appraisal). Available from: <https://www.cadth.ca/sites/default/files/pdf/htis/july-2012/RC0368%20Cannabinoids%20Final.pdf>
9. The use of medical marijuana: guidelines and recommendations [Internet]. Ottawa: CADTH; 2013 Jan 15 [cited 2016 Dec 12]. (Rapid response report: reference list). Available from: <https://www.cadth.ca/sites/default/files/pdf/htis/jan-2013/RA0611%20Medical%20Marijuana%20Final.pdf>
10. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* [Internet]. 2007 [cited 2017 Jan 10];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>

11. Wilkinson ST, Radhakrishnan R, D'Souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. *J Clin Psychiatry* [Internet]. 2016 Aug [cited 2016 Dec 9];77(8):1050-64. Available from: http://www.psychiatrist.com/JCP/article/_layouts/ppp.psych.controls/BinaryViewer.ashx?Article=/JCP/article/Pages/2016/v77n08/v77n0818.aspx&Type=Article Registration required.
12. Authorizing dried cannabis for chronic pain or anxiety: preliminary guidance [Internet]. Mississauga (ON): College of Family Physicians of Canada; 2014 [cited 2016 Dec 12]. Available from: http://www.cfpc.ca/uploadedFiles/Resources/_PDFs/Authorizing%20Dried%20Cannabis%20for%20Chronic%20Pain%20or%20Anxiety.pdf
13. Tilray. Evaluating safety and efficacy of cannabis in participants with chronic posttraumatic stress disorder. 2015 Jul 31 [cited 2016 Dec 12; Last updated: 2016 Nov 23]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: <https://clinicaltrials.gov/ct2/show/NCT02517424> Identifier: NCT02517424.
14. Multidisciplinary Association for Psychedelic Studies. Study of four different potencies of smoked marijuana in 76 veterans with chronic, treatment-resistant PTSD. 2016 Apr 29 [cited 2016 Dec 12; Last updated: 21 Jul 2016]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: <https://clinicaltrials.gov/ct2/show/NCT02759185> Identifier: NCT02759185.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wilkinson, ¹¹ 2016, United States	1 RCT	10 male soldiers with PTSD and treatment resistant nightmares	Nabilone, range: 0.5 mg to 3 mg	Placebo	Nightmares, sleep difficulties 16 weeks (7 weeks, 2 week washout, 7 weeks other study treatment)
	2 retrospective chart reviews	104 adult male offenders with serious mental illness, 90% with PTSD; 91% with marijuana dependence	Nabilone, range: 0.5 mg to 6 mg daily	None	Nightmares, hours of sleep; improvement in symptoms 11.2 weeks (mean)
		47 PTSD patients with treatment resistant nightmares	Nabilone, range: 0.5 mg to 6 mg (adjunctive)	None	Nightmares, sleep time, sleep quality, flashbacks, night sweats 12 months
	3 prospective open label trials	10 chronic PTSD patients	Oral THC, range: 2.5 mg to 5 mg daily (adjunctive)	None	CAPS Arousal Score; sleep quality (PSQI, NES), frequency of nightmares, CGI 3 weeks
		29 male combat veterans	Smoked marijuana ad lib	None	CAPS total score 16, 28, and 44

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
		80 military personnel with PTSD	(approximately 23% THC; < 1 % CBD (adjunctive) Smoked marijuana, approx. 2 g to 3 g per day	None	weeks QoL; pain scores; CAPS; discontinuation/ lowering of painkillers/ sedative dose 2 years

CAPS = Clinician Administered PTSD Scale; CBD = cannabidiol; CGI = Clinical Global Impressions scale; NES = Nightmare Effects Scale; PSQI = Pittsburgh Sleep Quality Index; PTSD = Post Traumatic Stress Disorder; QoL = Quality of Life; RCT = randomized controlled trial; THC = Tetrahydrocannabinol

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Systematic Reviews and Meta-Analyses using Amstar¹⁰

Strengths	Limitations
Wilkinson, ¹¹ 2016	
<ul style="list-style-type: none"> • An a priori research question was provided. • A satisfactory number of keywords were provided as search terms. • Additional studies or conference proceedings were identified through reference cross-checking. • The number of articles excluded was provided, with two reasons for exclusion provided. • The scientific quality of the included studies was thoroughly assessed and documented using the GRADE system. • The study outcomes were described narratively, which appeared to be appropriate given the significant heterogeneity of the included studies. • Potential conflicts of interest and funding sources were fully disclosed and resolved for the systematic review authors. 	<ul style="list-style-type: none"> • No explicit inclusion and exclusion criteria were stated aside from publication dates. • It was not stated whether two investigators selected studies or extracted data. • Only one database was searched (MEDLINE). • Very limited details regarding the characteristics of the included studies were provided. • A list of excluded studies was not provided. • It did not appear that publication bias was assessed. • Potential conflicts of interest were not reported for the included studies.

APPENDIX 4: Main Study Findings and Author’s Conclusions

Table A3: Summary of Findings of Included Studies	
Main Study Findings	Author’s Conclusions
Wilkinson, ¹¹ 2016	
<p>Nabilone versus placebo (n=1)</p> <p>Efficacy</p> <ul style="list-style-type: none"> • Significant improvement in nightmares (CAPS Recurrent Distressing Dreams item, $P = 0.03$) • CGI ($P = 0.05$) • WBQ ($P = 0.04$); • No difference on the CAPS Difficulty Falling or Staying Asleep item <p>Nabilone (no comparator, n=2)</p> <p><u>Study 1</u></p> <ul style="list-style-type: none"> • Significant decrease in nightmares ($P < 0.001$) • PCL-C ($P = 0.001$) • Significant increase in hours of sleep ($P < 0.001$) • GAF ($P = 0.001$) <p><u>Study 2</u></p> <ul style="list-style-type: none"> • 72% of sample reported subjectively that they had cessation of nightmares or a significant reduction in nightmare intensity • Subjective improvement in sleep time and sleep quality • Reduction of daytime flashbacks and night sweats <p>Adverse events:</p> <ul style="list-style-type: none"> • Nabilone was discontinued in 28% of patients in Study 2 due to side effects (not described); • No other adverse advents were reported 	<p><i>“There are few RCTS with medical marijuana or cannabinoids for psychiatric indications. The strength of the evidence for the use of medical marijuana for psychiatric indications of PTSD, Tourette’s disorder, and agitation in Alzheimer’s disease is very low at the present time.” (p. 1061).</i></p>

<p>Smoked Marijuana (n=2)</p> <p><u>Study 1</u></p> <ul style="list-style-type: none">• Significant decrease in CAPS total score (no <i>P</i> value provided) <p><u>Study 2</u></p> <ul style="list-style-type: none">• Improvement in QoL and pain scores and CAPS• Discontinuation/lowering of dose of sedatives and painkillers (no <i>P</i> value provided)	
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CAPS = Clinician Administered PTSD Scale; CGI = Clinical Global Impressions scale; GAF = Global Assessment of Functioning; PCL-C = Posttraumatic Stress Disorder Checklist – Civilian version; PTSD = Post-Traumatic Stress Disorder; WBQ = General Well-Being Questionnaire