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SUMMARY WITH CRITICAL APPRAISAL

Nabilone for the Treatment of Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

CAPS	Clinician Administered PTSD Scale
CASP	Critical Appraisal Skills Programme
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CBT	Cognitive behavioural therapy
CGI-C	Clinical Global Impression of Change
CRD	Centre For Reviews and Dissemination
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (4th ed., Text Revision)
EMDR	Eye movement desensitization and reprocessing
GAF	Global Assessment of Functioning
HTA	Health Technology Assessment
PCL-C	Posttraumatic Checklist – Civilian version
PTSD	Post-traumatic stress disorder
RCT	randomized controlled trial
SD	Standard deviation
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TF-CBT	Trauma-focused cognitive behavioural therapy
WBQ	Well-being questionnaire

Context and Policy Issues

Post-traumatic stress disorder (PTSD) is characterized by substantial psychological or physiological distress following exposure to trauma.[1] According to the most recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria for PTSD diagnosis includes either direct, or indirect (e.g., as a witness, or having learned that a close family member or friend has experienced a traumatic event), exposure to situations of actual or threatened death, violence, sexual assault, or serious injury. Individuals with PTSD have at least one intrusion symptom defined as recurrent, involuntary nightmares, flashbacks, and/or psychological or physiological distress at reminders of the trauma, lasting for greater than one month.[1,2] These intrusive and distressing symptoms have a significant effect on a person's quality of life, often leading to persistent avoidance of stimuli associated with the trauma, negative alterations in cognition, detachment from others, distorted blame, irritability, aggressive or reckless behavior, and sleep disturbances.[1] Approximately 75% of individuals with PTSD have comorbid psychiatric disorders such as major depressive disorder, substance abuse disorder, and/or alcohol dependence.[3] Suicidality increases in the PTSD population approximately 2 to 3-fold and odds of lifetime suicide attempts increase with the presence of comorbid conditions.[4] Economically, PTSD is associated with more frequent and longer hospitalizations, in addition to a greater utilization of mental health services.[5]

Lifetime prevalence of PTSD in Canada was estimated at 9.2%, with one-month prevalence rates being more than double in women (3.4%) versus men (1.3%), according to a national survey conducted in 2002.[3] Approximately, 76% of Canadians in the survey reported exposure to at least one significantly traumatic event in their lifetime most commonly reported as the sudden death of a loved one, sexual assault, and seeing someone badly injured or killed.[3] The majority (68.5%) of individuals reported symptoms of PTSD lasting for more than a year.[3]

Treatment for PTSD is generally centered on education and psychological therapies (with or without pharmacological intervention) mainly cognitive behavioral therapy (CBT) protocols, such as trauma-focus CBT (TF-CBT), or eye movement desensitization and reprocessing (EMDR) therapeutic techniques.[1,6] According to the Anxiety Disorders Association of Canada/Association Canadienne des troubles anxieux Canadian clinical practice guidelines, first line pharmacological intervention calls for the use of antidepressants classified as selective serotonin re-uptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine) or serotonin and norepinephrine re-uptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine).[1] Second line and third line agents include additional antidepressants demonstrating less clinical efficacy (e.g., fluvoxamine, mirtazapine), with third line agents including anticonvulsant (e.g., topiramate, lamotrigine) and atypical antipsychotic drugs (e.g., risperidone, aripiprazole).[1] Currently, synthetic cannabinoids are not listed within the Canadian guidelines for treatment of PTSD.

Nabilone is a synthetic cannabinoid that activates Cannabinoid receptor type 1 (CB1) cell receptors (abundantly expressed in the central nervous system), and has previously been approved for the treatment of nausea and vomiting induced by chemotherapy treatments in Canada for over 30 years.[7-9] The first open label study of nabilone, demonstrated positive outcomes in the treatment of PTSD related symptoms.[7] The majority of study participants (72%) reported total cessations or lessening of severity of recurrent nightmares, a hallmark symptom of PTSD.[7] Additionally, some study participants noted reduction in PTSD-related flashbacks, and improved sleep time with mild to moderate side effects.[7]

The current Rapid Response Report is an update to a previous CADTH Rapid Response Report[10] and will seek to identify and synthesize the evidence around the clinical effectiveness, and evidence-based guidelines for nabilone treatment for PTSD.

Research Questions

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

Key Findings

Overall, two primary clinical studies, including one randomized controlled trial and one non-randomized study, were identified with outcomes related to the clinical effectiveness of nabilone for subjects with post-traumatic stress disorder. The limited evidence identified, shows that nabilone improved post-traumatic stress disorder related symptoms (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). In particular, significant reduction of nightmares, and improvement in sleep time and quality were observed. The included study populations were 100% male and comprised of either active military personnel, or institutionalized inmates, thereby limiting the generalizability of the results. Currently, there is a lack of available evidence for the clinical effectiveness of nabilone for the treatment for post-traumatic stress disorder.

No guidelines informing the use of nabilone for treatment of post-traumatic stress disorder were identified.

Methods

Literature Search Methods

This report makes use of a literature search developed for a previous CADTH report.[10] The original literature search was conducted in October 2018 on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2013 and October 2, 2018. For the current report, database searches were rerun on January 17, 2019 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since October 2018.

Selection Criteria and Methods

One reviewer screened citations and selected relevant studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant citations 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 a diagnosis of post-traumatic stress disorder
Intervention	Nabilone (Cesamet)
Comparator	Q1: Active treatments, placebo, or not treatment Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., decreased symptoms, improved quality of life) and safety (e.g., harms, adverse events, abuse and misuse) Q2: Guidelines
Study Designs	Q1: HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies Q2: Guidelines

HTA = Health Technology Assessment

Exclusion Criteria

Citations were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to January 1, 2013. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The RCTs and non-randomized studies included after full-text screening were critically appraised using the Critical Appraisal Skills Programme (CASP) checklist.[11,12] Summary scores were not calculated for the included studies, rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 63 citations were identified in the literature search. Following screening of titles and abstracts, 46 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. Seven potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 22 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised one RCT and one non-randomized study. Appendix 1 presents the PRISMA[13] flowchart of the study selection.

Summary of Study Characteristics

One RCT and one non-randomized retrospective chart review study were included in this Rapid Response Report.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two primary clinical studies met the inclusion criteria outlined in Table 1. The first study was an RCT[14] which utilized a crossover design. The intervention was 16 weeks in length and was comprised of two periods.[14] Period 1 was seven weeks in duration in which participants were assigned to either nabilone or placebo.[14] Period 1 was followed by a two-week washout period.[14] Thereafter, participants crossed over to Period 2 for seven weeks where they were assigned to the opposite intervention received during Period 1.[14] The second study included was a non-randomized retrospective chart review which examined the use of nabilone in a correctional facility for symptoms of insomnia and nightmares related to PTSD between January 1, 2010 to July 31, 2013.[9]

Country of Origin

The included studies were both conducted in Canada.[9,14]

Patient Population

The RCT[14] was conducted in a sample of 10 male military soldiers with a current diagnosis of PTSD as per the DSM-IV-TR, and treatment resistant nightmares. The non-randomized study[9] was conducted in 104 adult, male offenders hospitalized with serious mental illness, approximately 90% of which, were diagnosed with 'PTSD or similar' which included insomnia and nightmare disorders not exclusively associated with PTSD. Additionally, many of the subjects had multiple comorbid conditions such as anxiety (~95%), various mood disorders (~65%), major depressive disorder (~40%), substance/alcohol abuse (~95%), and reported prior alcohol and/or cannabis use (~55% and ~90%, respectively). [9] Of the 104 included subjects, 58 (56%) were identified as being followed and measured for PTSD symptoms.

Interventions and Comparators

The RCT reported nabilone dosages were started at 0.5 mg and titrated weekly to a maximum of 3.0 mg.[14] Titration took place over a total of five weeks, resulting in consistent

dosing of nabilone for the last two weeks of intervention.[14] Eight out of nine subjects and three out of ten subjects met the maximum dosing for the placebo and nabilone groups, respectfully, (mean ± standard deviation [SD] dose for placebo group: 2.78 ± 0.7 mg andnabilone group 1.95 ± 0.9 mg).[14] The placebo group for both Period 1 and Period 2 of the trial received placebo tablets for all seven weeks.[14] In the non-randomized study, initial mean dosages of nabilone were 1.4 mg (range: 0.5 mg to 2.0 mg) daily, with 1.4 mg final dosage of 4.0 mg (range: 0.5 mg to 6.0 mg) daily.[9] All nabilone was prescribed off label *de novo,* ranging from one day to 36 weeks with a mean treatment duration of 11.2 weeks (range: 1 day to 36 weeks).[9] There were no comparators evaluated in the non-randomized study.

Outcomes

The main outcomes reported for the two studies captured in this Rapid Response Report were the effectiveness of nabilone in the treatment of insomnia and nightmares related to PTSD via both clinically validated self-reported questionnaires, and self-reported diary logs. Symptoms, comorbid conditions, and adverse events were monitored and reported objectively by study staff, or through medical chart review, during the use of nabilone.

The RCT[14] utilized a variety of clinical questionnaires to measure differences in pre- and post-test scores at the beginning and end of each period of the trial. The primary outcome related to the frequency of PTSD associated nightmares, was measured by the Clinician-Administered PTSD Scale (CAPS) Reoccurring and Distressing Dream Item- Frequency and Intensity questionnaire. Frequency items within the CAPS Reoccurring and Distressing Dream Item are scored from 0= 'never' to 4= 'daily or almost every day', and Intensity items are scored from 0= 'none' to 4= 'extreme'. Other clinical outcomes associated with self-reported improvement included, the Clinical Global Impression of Change (CGI-C) (score of 1= very much improved and score of 7= very much worse), and the General Well Being Questionnaire (WBQ) (maximal well-being score= 100). In addition to these clinician-administered, self-reported questionnaires, trial participants were asked to keep a Sleep Diary Log recording total sleep time and numbers of awakenings each night.

The primary outcomes reported in the non-randomized study[9] were comparisons of self-reported sleep hours per night, and nights with nightmares per week, measured pre and post nabilone treatment. Additional outcomes were captured using clinically validated questionnaires pre and post nabilone treatment to assess PTSD symptoms and global functioning using the Posttraumatic Checklist-Civilian version (PCL-C) and the Global Assessment of Functioning (GAF), respectively. Overall, 58 subjects were assessed for PTSD symptoms pre and post nabilone treatment utilizing the PCL-C questionnaire. The PCL-C questionnaire is the civilian version of the 17-item checklist measuring the DSM-IV symptoms related to PTSD. Symptoms are scaled in severity with a response of 1 ('Not at all') through 5 ('Extremely'), providing an overall score range of 17-85. Questions include topics related to falling or staying asleep, in addition to reoccurring nightmares.[15]

Summary of Critical Appraisal

Critical appraisal was performed utilizing the CASP checklists for RCTs and cohort studies for the two respective studies captured in this review.[11,12] The following is a summary that highlights the strengths and limitations from each study, any additional details are provided in Appendix 3.

Both studies addressed a clearly focused issue. However, both studies utilized a single site study design within a specific population, therefore the generalizability of results is limited.

Strengths of the RCT[14] include, effective randomization of treatment groups, blinded study personnel (both investigators and subjects), all subjects were accounted for at the end of the trial (although one patient did not finish and was documented as 'moving facilities' and therefore accounted), and consideration of important clinical outcomes. Limitations of the study included, small sample size (*n*=10), results that were not precise (i.e., large SDs), no comparison of baseline characteristics, and due to the crossover design, uncertainty if the 2-week washout period was adequate and/or had any influence on the outcomes.

Strengths of the non-randomized retrospective chart review[9] include, that all subjects were identified in a reproducible way, exposures were accurately measured to minimize bias, and patient data was complete. Limitations of this study included, lack of confounder assessment, outcomes that were measured using self-report, short duration of patient follow-up, due to institutional treatment center discharge, mix of study population, and crude statistical methods were applied (i.e., confounding factors were collected but not evaluated).

Summary of Findings

The summary of findings are presented according to the research questions posed by this Rapid Response Report. Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Nabilone

Both of the included clinical studies captured in this Rapid Response Report found that nabilone was an effective treatment for symptoms related PTSD. Specifically, an RCT provided evidence to support the use of nabilone for PTSD-related nightmares, reporting a significant reduction in the frequency of nightmares with nabilone treatment versus placebo.[14] A non-randomized study reported a significant decrease in PTSD symptomatology (including measures of insomnia and nightmares) via clinically validated PCL-C questionnaire scores.[9] The need for further investigation regarding the clinical effectiveness of nabilone in PTSD was recommended by both studies specifically citing the need for replication of the study findings and/or a more comprehensive examination of symptomatology related to PTSD.

Overall, ten males participated in the RCT,[14] nine of which, were followed to completion. A significant improvement from baseline, was reported in all three questionnaires (CAPS, CGI-C, and WBQ), when trial participants were treated with nabilone versus treatment with placebo. Treatment with nabilone led to a reduction in the frequency of nightmares (nabilone (mean ± standard deviation (SD)): -3.6 ± 2.4 versus placebo: -1.0 ± 2.1, p=0.03), an improvement in mean CGI-C scores (nabilone: 1.9 ± 1.1 versus placebo: 3.2 ± 1.2, p=0.05), and an improvement in WBQ mean scores (nabilone: 20.8 ± 22.1 versus placebo: -0.4 ± 20.6, p=0.04). Rebound and carry-over effects following the washout period were not detected. No significant effect was observed on sleep quality and quantity, as measured by CAPS, difficulty falling and staying asleep items, or Sleep Diary (nabilone mean: 7.6 ± 1.9 hours versus placebo 7.4 ± 2.0 hours, p=0.97). The most common adverse events in the nabilone group were dry mouth and headache. Possibly due to the mild nature of the adverse events reported, nabilone was described by the authors as well-tolerated with 50% of participants receiving nabilone, versus 60% receiving placebo, reporting adverse events.

Unfortunately, the type of adverse events experienced in the placebo group were not reported which limits the interpretation of these findings.

The non-randomized study,[9] reported a significant decrease in mean PCL-C scores pre and post nabilone treatment (pre: 54.7 ± 13.0 versus post: 38.8 ± 7.1, p=0.001). The change in PCL-C scores signify a reduction in PTSD symptoms, from moderate to borderline-mild symptoms. The assessment of self-reported sleep hours per night, nights with nightmares per week, and GAF scores were not captured specifically in the 58 individuals who were assessed for PTSD symptoms. However, of note, for the 101 subjects treated with insomnia (not exclusively related to PTSD but included some or all of the 58 individuals with PTSD), a significant increase in the mean number of hours slept pre and post nabilone treatment was reported (pre: 5.0 ± 1.4 versus post: 7.2 ± 1.2, p<0.001). Additionally, for the 90 subjects treated for nightmares (not exclusively associated with PTSD, but including PTSD subjects), a significant reduction was reported in the mean number of nights per week in which nightmares were experienced pre versus post nabilone treatment (pre: 5.2 ± 2.2 versus post: 0.9 ± 1.8, p<0.001).

In the non-randomized study, nabilone was reported to be well-tolerated by the study authors, possibly due to the mild nature of the adverse events, with 31 (29.8%) of the study subjects reporting adverse events, including 10 who withdrew from the treatment. The most commonly reported adverse effects were sedation (12.5%), dry mouth (6.7%), and feeling 'stoned' (3.8%). Psychosis was reported in two individuals (2%) with a previous medical history of psychosis.

Guidelines

No relevant guideline evidence regarding the use of nabilone for PTSD was identified.

Limitations

There are several limitations that should be noted. First, no clinical guidelines describing best practices or recommendations for the use of nabilone for PTSD were identified. Second, only one RCT and one non-randomized study were identified for inclusion in this Rapid Response Report.[9,14] Both studies captured in this review were conducted in a single center, and the populations sampled provide limited generalizability to the overall PTSD population in Canada. Specifically, both studies were comprised of 100% male subjects. The RCT[14] population included a small sample of active military personnel, and the non-randomized study[9] consisted of institutionalized male inmates, the majority of which had comorbid psychological and/or substance/alcohol abuse disorders. Due to the mixing of a 'PTSD and similar' populations in the non-randomized study, specific measures regarding insomnia and nightmares were unable to be captured for the PTSD population exclusively.[9] Additionally, neither study evaluated the efficacy of nabilone against any active, first-line comparators. Therefore, the evidence base for the clinical effectiveness of nabilone for the treatment of PTSD requires further research in order to be strengthened.

Conclusions and Implications for Decision or Policy Making

Overall, two primary clinical studies (one RCT and one non-randomized study) were identified to address the research questions in this Rapid Response Report. While the available evidence suggests that treatment with nabilone improved general PTSD symptoms (based on the DSM-IV criteria), particularly the reduction of nightmare occurrence, further research is needed understand the clinical effectiveness of nabilone for the overall PTSD condition.

Current treatment practices for PTSD involve the use of antidepressants, anticonvulsants, and atypical antipsychotics with the objective of modulating neurotransmitter release in the brain. Nabilone is a synthetic cannabinoid that activates the CB1 receptor, of the endocannabinoid system, the most abundantly expressed receptor in the brain.[8] CB1 modulates neurotransmitter release (e.g., serotonin, glutamate, dopamine) and mediates glucocorticoid action to consolidate aversive memories.[8]

Two CADTH Rapid Response Reports regarding the clinical effectiveness and safety of long-term nabilone use,[16] and the clinical effectiveness of medical marijuana for PTSD (including synthetic cannabinoids)[17] have been previously published. The questions posed in the current Report are similar to the Rapid Response Report on medical marijuana (January 2017) due to the PTSD population included.[17] The prior Report, identified a single systematic literature review by Wilkinson et al. from the United States, which included studies by Fraser et al.,[7] Cameron et al.,[9] (the non-randomized study captured in this report) and Jetly et al.,[14] (the RCT captured in this report) as well as two additional studies evaluating smoked cannabis.[18] Due to a mixed population and treatments, the Wilkinson et al. systematic review was not included in this report and instead the individual citations were assessed for inclusion. Although the Fraser et al.[7] study was excluded due to the publication date not meeting criteria; it is important to mention that both the Jetly et al.[14] and Cameron et al.[9] studies confirm the original results presented by Fraser et al.[7] regarding the effectiveness of nabilone in the treatment of nightmare reduction related to PTSD.

Limitations notwithstanding, the evidence captured in this Rapid Response Report confirms previously reported reductions in the frequency of nightmares, and the improved quality and duration of sleep in individuals with PTSD with treatment of nabilone. In one study, nabilone was demonstrated to reduce, or allow the discontinuation, of commonly used first- and second-line drugs (e.g., antidepressants, anticonvulsants, sedatives) associated with potentially severe adverse events (e.g. suicidality). Although a large proportion of study participants reported experiencing adverse events, nabilone was noted as well-tolerated by study authors and the severity of these events were mild/moderate in nature (e.g. dry mouth), with the exception for individuals with a previous medical history of psychosis. Furthermore, nabilone does not produce a positive urine test, does not significantly alter mood state after a single dose, has low potential for the development of tolerance, and does not retain any street value; making the potential abuse potential of nabilone low.[19] Additional clinical trials or observational studies comparing nabilone against active, first-line comparators in the treatment of symptoms associated with PTSD, would strengthen the evidence for use in this population.

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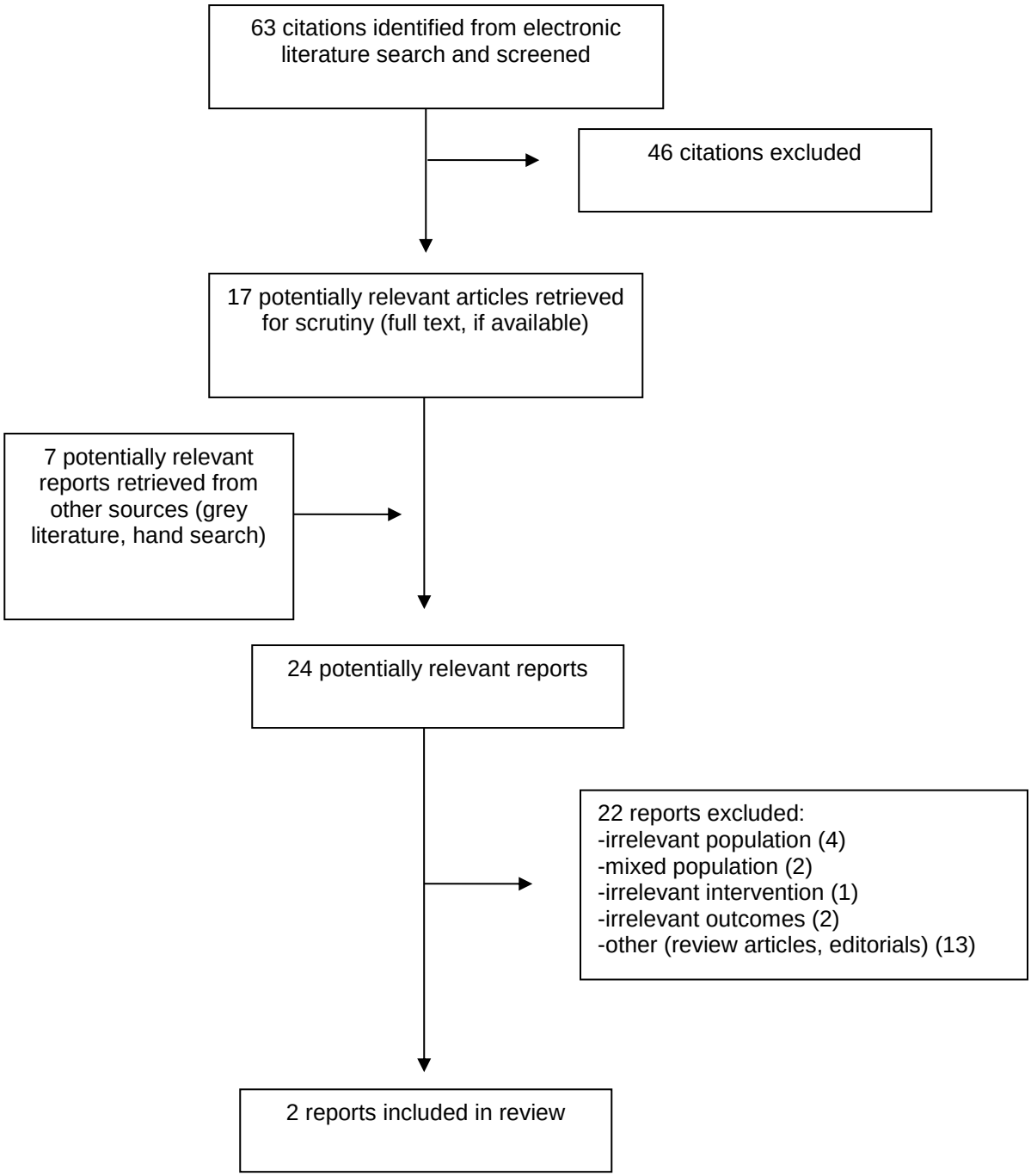
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Jetly et al., 2015, Canada	Randomized (1:1), double-blind placebo-controlled cross-over design with a 2-week washout between periods (each lasting 7 weeks)	10 male soldiers (mean age=43.6±8.2 years; range 18-65 years) with a current diagnosis of PTSD as per the DSM-IV-TR and treatment resistant nightmares	Intervention: Nabilone tablets, dosage started at 0.5 and titrated weekly to a maximum of 3.0 mg Comparator: Placebo tablets	CAPS Recurring and Distressing Dream Scores; CGI-C; WBQ; sleep disturbances (total sleep time and number of awakenings each night); adverse effects and vital status A total of 16 weeks for follow-up
Cameron et al., 2014, Canada	Retrospective chart review	104 adult male offenders (mean age=32.7 years; range 19-55 years); 90% with PTSD or similar; 58 completed the PCL-C No prior use of nabilone	Intervention: Nabilone, initial dosage range: 0.5-2.0 mg daily, and final dosage range: 0.5-6.0 mg daily; mean length of nabilone was 11.2 weeks (range: 1 day – 36 weeks) Comparator: None	PCL-C; Nightmares, hours of sleep; Axes I-III diagnoses; GAF; pain severity; adverse effects, medication discontinuation; abuse concerns (raised by staff) Follow-up was based on inpatient hospital stay and nabilone use (mean=11.2 weeks)

CAPS = Clinician Administered PTSD Scale; CGI-C = Clinical Global Impression of Change; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders (4th ed., Text Revision); GAF = Global Assessment of Functioning; PCL-C = Posttraumatic Checklist – Civilian version; PTSD = posttraumatic stress disorder; WBQ = Well Being Questionnaire

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using CASP[11,12]

Strengths	Limitations
Jetly et al., 2015[14]	
- **Addressed a clearly focused issue** - **Randomized to treatment groups effectively** - **Study personnel (investigators and subjects) were blinded** - **All subjects were properly accounted for at end of the trial** - **All clinically important outcomes were considered**	- Single-centre study, may not be generalizable to other centres - Population was very specific (i.e., military soldiers), may not be generalizable to other centres - Results were not precise (although significant) - Groups were not compared for similarities and differences at the start of the trial - Crossover study design - Precision of the outcome estimates were lacking, due to the sample size
Cameron et al., 2014[9]	
- **Addressed a clearly focused issue** - **Cohort was identified in a reproducible way** - **Exposures were measured accurately to minimize bias** - **Follow-up of subjects was complete**	- Single-centre study, may not be generalizable to other centres - Population of hospitalized subjecs, may not be generalizable to other centres - Mixed population was evaluated for some outcomes - Confounders not considered for data analysis - Crude statistical methods used - Some outcomes were measured using self-report and therefore may be subject to bias - Follow-up of subjects was based on discharge date and may not be long enough to appropriately assess outcomes

CASP = Critical Appraisal Skills Program

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Jetly et al., 2015[14]	
CAPS (Mean ± SD) **Nabilone -3.6 ± 2.4** **Placebo -1.0 ± 2.1** **P = 0.03** **CGI-C (Mean ± SD)** **Nabilone 1.9 ± 1.1** **Placebo 3.2 ± 1.2** **P = 0.05** **WBQ (Mean ± SD)** **Nabilone 20.8 ± 22.1** **Placebo -0.4 ± 20.6** **P = 0.04** **Sleep quantity through the Sleep Diary (Mean ± SD)** **Nabilone 7.6 ± 1.9** **Placebo 7.4 ± 2.0** **P = 0.97** **Treatment-related Adverse Effects** **Nabilone 50%** **Placebo 60%** **Most common adverse effects with nabilone were dry mouth and headache.**	*"This study gives added support for the potential use of synthetic endocannabinoids, such as nabilone as a medication for treatment of PTSD-related nightmares. However, these findings need to be replicated in a larger cohort. There is a need for further exploration of the effect of nabilone on other symptoms of PTSD such as re-experiencing, hypervigilance and insomnia." (p. 588)*[14]
Cameron et al., 2014[9]	
PCL-C scores (Mean ± SD) **Pretreatment 54.7 ± 13.0** **Posttreatment 38.8 ± 7.1** **P < 0.001** **Number of hours slept (Mean ± SD) [a]** **Pretreatment 5.0 ± 1.4** **Posttreatment 7.2 ± 1.2** **P < 0.001** **Number of nights per week with nightmares reported (Mean ± SD) [a]** **Pretreatment 5.2 ± 2.2** **Posttreatment 0.9 ± 1.8** **P < 0.001** **Treatment-related Adverse Effects[a]** **29.8% reported adverse effects, of which the most common were sedation (12.5%), dry mouth (6.7%) and "feeling stoned" (3.8%). Psychosis was the most serious adverse**	*"Prospective, randomized controlled studies comparing nabilone to placebo and to prazosin for PTSD-related insomnia and nightmares seem to be reasonable next steps, as well as looking at its effect on other PTSD symptoms. In addition, a randomized placebo-controlled study looking at nabilone for harm reduction also seems warranted. Other agents acting on the endocannabinoid system also seem to merit investigation. If our hypothesis is correct that cannabinoids can be safely and effectively used to target comorbid PTSD-related insomnia and nightmares, chronic pain, and harm reduction in cannabis-dependent individuals, the challenge faced by clinicians working with these often complex patients may become greatly facilitated." (p. 564)*[9]

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
effect (occurring in two subjects), although both subjects had preexisting psychotic illness.	

[a] Not exclusively associated with PTSD but including PTDS subjects

CAPS = Clinician Administered PTSD Scale; CGI-C = Clinical Global Impression of Change; PCL-C = Posttraumatic Checklist – Civilian version; PTSD = posttraumatic stress disorder; SD = standard deviation; WBQ = Well Being Questionnaire