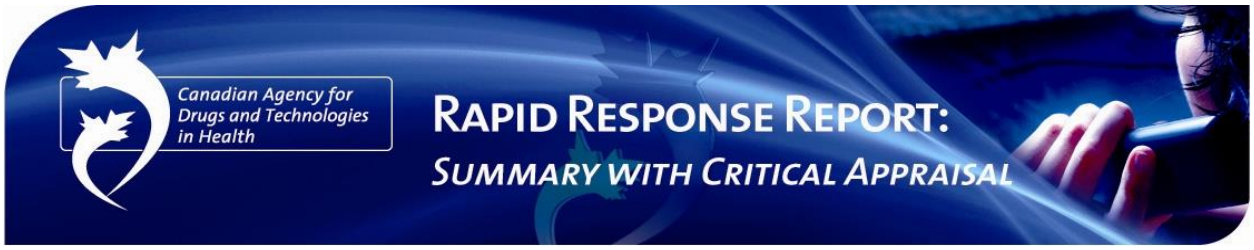

TITLE: Long-term Nabilone Use: A Review of the Clinical Effectiveness and Safety

DATE: 16 October 2015

CONTEXT AND POLICY ISSUES

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that occurs following a traumatic event involving death or serious injury or threat of death or serious injury.[1] The individual then persistently re-experiences the event through intrusion symptoms (such as recurrent, involuntary, and intrusive memories, traumatic nightmares), and may develop other symptoms such as avoidance behaviours (such as efforts to avoid activities, places, or people that arouse recollections of the trauma), negative alterations in cognitions and mood (such as inability to recall key features of the traumatic event), alterations in arousal (such as difficulty falling or staying asleep) and reactivity (such as exaggerated startle response).[1] The symptoms of PTSD cause significant distress and functional impairment. Based upon a representative sample of the Canadian population aged 18 years and over, the lifetime prevalence of PTSD was estimated to be approximately 9.2%, with 2.4% of the population currently having PTSD.[2]

Cannabis has been used medically for its antiemetic, sedative, and analgesic effects and for its ability to stimulate appetite.[3] The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol (THC).[3] Nabilone is a synthetic cannabinoid analog of THC[3] and 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.[4] For its approved indication, nabilone (1 mg to 2 mg) is used short-term, administered the night before and one to three hours prior to chemotherapy and can be continued up to 24 hours following chemotherapy. However, nabilone has also been used off-label for the management of nightmares associated with PTSD[5] and for other conditions, such as non-cancer related pain[6] and multiple sclerosis (MS).[7] Duration of treatment with nabilone for indications such as these is longer-term than for its approved indication, raising questions about its safety and efficacy with extended use.

The purpose of this Rapid Response report is to summarize the evidence of clinical efficacy and harms associated with evidence of efficacy and safety of long-term nabilone use in adult populations with PTSD and other chronic conditions.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of long-term nabilone use?

2. What is the evidence for the safety and harms of long-term nabilone use?

KEY FINDINGS

Based upon one systematic review and four RCTs, nabilone was more effective than placebo in improving PTSD-associated nightmares and quality of life, neuropathic pain related to MS and diabetes, and spasticity due to spinal cord injury for four to nine weeks of treatment. Adverse events were generally not considered serious. However, the generalizability of these results is uncertain given the limited number of participants in each trial.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Embase, 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 the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and September 18, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

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 taking nabilone
Intervention	Long-term (≥1 month) nabilone
Comparator	Short-term (<1 month) use, placebo, no comparator (for safety)
Outcomes	Continued clinical effectiveness with long term use, change in adverse effects over time (such as headache, dizziness, drowsiness, feeling “high”, weakness, lack of co-ordination, depressed mood, dry mouth, difficulty concentrating), safety and harms.
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), non-RCTs

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 2010.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised using the AMSTAR tool,[8] and randomized studies were critically appraised using Downs and Black Checklist.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

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 69 citations were identified in the literature search. Following screening of titles and abstracts, 37 citations were excluded and 32 potentially relevant reports from the electronic search were retrieved for full-text review. No publications were retrieved from the grey literature search. Of these potentially relevant articles, 27 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design

One systematic review[6] and four randomized controlled trials (RCTs)[7,10-12] met the inclusion criteria for this Rapid Response. No non-randomized studies met the inclusion criteria for the review. The RCTs differed in their designs, with two using cross-over designs[10,12] and two having parallel group designs.[7,11] One parallel-group study used an enriched-enrollment, randomized withdrawal design in which all patients received nabilone during a single-blind phase. Those patients who then met the criteria for the double-blind phase at the end of four weeks were then randomized to taper down and switch to placebo or to continue with nabilone.[11] The study duration ranged from four weeks up to nine weeks (Tables A1 and A2, Appendix 2).

Country of Origin

The systematic review was performed by authors from Canada.[6] All four of the included studies were conducted in Canada.[7,10-12] (Tables A1 and A2, Appendix 2).

Patient Population

The systematic review included 18 studies in total, three of which were studies of nabilone in adults with chronic pain syndromes such as fibromyalgia or spasticity-related pain, with sample sizes ranging from 13 to 40 participants[6] (Tables A1, Appendix 2). One RCT included adult male patients with PTSD who experienced nightmares that were related to trauma.[10] The remaining

three studies included patients with chronic pain due to multiple sclerosis,[7] spinal cord injury,[12] and diabetic (Table A2, Appendix 2).

Interventions and Comparators
In the systematic review,[6] the dose of nabilone ranged from 0.25 mg to 2.0 mg per day and was compared with placebo (Tables A1, Appendix 2). In the included RCTs, nabilone was compared with placebo and was dosed flexibly, ranging from 0.5 mg to 3.0 mg per day, with dose titration according to therapeutic and adverse effects. (Table A2, Appendix 2).

Outcomes
The included systematic review reported on pain and adverse effects[6] while the included RCTs used questionnaires and scales to assess symptoms such as pain, spasticity and recurring and distressing dream scores.[7,10-12] Limited information on adverse effects was reported in the studies (Table A2, Appendix 2).

Summary of Critical Appraisal
Based on the AMSTAR assessment, the included systematic review appeared to be rigorous in design in terms of the search strategy and quality assessment,[6] with detailed reporting of the characteristics of the included studies and their populations and a narrative summary of results. The narrative summary appeared to be an appropriate approach given the differences in the study populations of the identified studies (i.e., patients with many different underlying painful conditions). Study selection was performed by a single reviewer and reporting of outcome data was somewhat limited, focusing mainly on the measurement of pain (Table A3, Appendix 3).[6]

The included RCTs provided sufficient detail to meet most of the Downs and Black checklist items related to reporting. Three of the RCTs reported limited details about the demographic and clinical characteristics the included patients, and details of adverse events were sparse.[7,10,12] Some internal validity items were not met, with lack of detailed reporting of methods of randomization or allocation concealment and adherence to study medication. As well, there was a risk of unblinding due to the adverse effects of nabilone (such as sedation and dizziness). The efficacy outcomes were clearly reported and measured using standard scale measures.[7,10-12] External validity could potentially be limited by extensive exclusion criteria, but all included RCTs were conducted in Canada, which may improve generalizability to Canadian practice. The use of co-interventions may also impact the external validity of the studies, with nabilone being an add-on treatment to gabapentin in one study,[7] and other treatments being permitted in another.[10] As well, given the limited numbers of patients included in each trial, it is unclear if these selected populations would be representative of the target population (Table A4, Appendix 3).

Summary of Findings

1. What is the clinical effectiveness of long-term nabilone use?

Systematic Review

The systematic review briefly summarized pain outcomes narratively for each study selected for inclusion, three of which assessed the efficacy of nabilone in different chronic pain syndromes. In one RCT of nabilone in patients with fibromyalgia, the use of nabilone was associated with statistically significant improvements in pain and in scores on the Fibromyalgia Impact Questionnaire (FIQ), a measure of functioning, mental health, and pain, relative to placebo. In

an RCT of patients with spasticity due to upper motor neuron syndrome, nabilone decreased pain related to spasticity but did not improve performance of activities of daily living (ADLs). In an RCT of patients with chronic spinal pain, nabilone decreased the intensity of spinal pain. (Table A5, Appendix 4).Based on these findings, the review authors concluded that cannabinoids were moderately effective for the treatment of chronic, non-cancer pain, but that larger, long-term studies were needed. No conclusions specific to the use of nabilone were made.

Randomized Controlled Trials

In one of the four included RCTs, the efficacy of nabilone in comparison with placebo was assessed in 10 patients with PTSD over a seven-week treatment period.[10] Statistically significant improvements in Clinician-Administered PTSD Scale Recurring and Distressing Dream scores and in scores on the General Well Being Questionnaire were observed. The difference between placebo and nabilone on the Clinician Global Impression of Change was not statistically significant. The authors concluded that these results supported the use of nabilone for PTSD related nightmares, but that replication was needed in a larger patient group (Table A6, Appendix 4).

The remaining three RCTs assessed the efficacy of nabilone for chronic conditions associated with pain or spasticity.[7,11,12] In 15 patients with MS-induced neuropathic pain, the efficacy of nabilone was assessed as add on therapy to gabapentin after nine weeks of treatment.[7] The intensity of pain improved at a faster rate with nabilone over the nine-week period than with placebo, with visual analog scale (VAS) scores reflecting lower average levels of pain. Based on the Patient-rated Global Impression of Change, 100% of patients treated with nabilone reported some improvement compared with 43% of patients treated with placebo ($P < 0.05$) (Table A6, Appendix 4). It was concluded that nabilone was effective as add on therapy to gabapentin for the management of pain in MS.

In 26 patients with diabetic peripheral neuropathic pain, nabilone was more effective than placebo for improving pain and sleep disturbance after five weeks of treatment.[11] Improvements in anxiety, quality of life (EQ-5D score), and sleep scores with nabilone relative to placebo were reported, but differences in depression were not statistically significant. The authors concluded that nabilone was effective for the management of diabetic peripheral neuropathic pain and improved quality of life and sleep (Table A6, Appendix 4).

In patients with spinal cord injury and spasticity, nabilone improved some measures of spasticity, but not the frequency of spasm.[12] Change in the Clinical Global Impression (CGI), a single-item scale that rates the severity of illness based upon the judgement of a clinician, was not statistically significant during treatment with nabilone relative to placebo. The authors concluded that the results suggested nabilone improved spasticity, but that larger studies with longer treatment duration were needed (Table A6, Appendix 4).

2. What is the evidence for the safety and harms of long-term nabilone use?

Systematic Review

The most common adverse effects of nabilone were listed, without reporting of the proportions of participants who experienced that adverse effect.[6] Central nervous system effects (dizziness, drowsiness, fatigue) were reported in the three relevant studies that included nabilone (Table

A5, Appendix 4).No details were provided with respect to the timing, resolution or persistence of adverse effects with continued treatment or the adverse effect rates in the placebo treated patients in the included studies. The systematic review authors did not make specific conclusions with respect to short or long-term safety of nabilone.

Randomized Controlled Trials

The prevalence of any treatment emergent adverse effect with nabilone and placebo was reported in two studies (Table A6, Appendix 4). In one cross-over trial of patients with PTSD, adverse effects were reported in 50% of patients during the nine-week treatment with nabilone and 60% of patients during treatment with placebo, with the most common adverse effects with nabilone being dry mouth and headache.[10] In a parallel group study in patients with neuropathic pain, the prevalence of adverse effects was similar to the study in PTSD, with 46% of placebo and 54% of nabilone-treated patients reporting one or more adverse event.[11] The most common adverse effects with nabilone included dizziness, dry mouth, drowsiness, confusion, impaired memory, and lethargy.[11] In the second parallel group study of patients with multiple sclerosis, the most common adverse events with nabilone were reported but not with placebo. Drowsiness and dry mouth affected 63% and 50% of patients, respectively.[7] In the other cross-over trial, 73% of patients with spinal cord injury reported adverse effects while taking nabilone, the most common being drowsiness, dry mouth, asthenia, and vertigo.[12]

Limitations

While one systematic review and four RCTs provided evidence of efficacy and safety of nabilone, there was a lack of evidence extending beyond nine weeks of treatment. Thus, the durability of treatment response with nabilone over a longer period time is unknown. No studies comparing long-term treatment and short-term treatment with nabilone were identified so this remains an evidence gap. Further, only one study included patients with PTSD, which was a condition of particular interest in the Rapid Response. It is unclear if evidence of long-term safety of nabilone in other conditions could be generalized to the PTSD population. Moreover, given the limited number of participants in each study, the representativeness of the study sample is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on evidence from one systematic review and four small RCTs, nabilone appeared to be safe and efficacious for the treatment of PTSD-associated nightmares, and for pain and spasticity for up to nine weeks of treatment. However, evidence of safety and efficacy beyond nine weeks is currently lacking. Patients with PTSD reported improvements in distressing nightmares and well-being while undergoing treatment with nabilone relative to treatment with placebo.[10] Improvements in pain and quality of life were also observed in other conditions.[7,11,12] While adverse effects were common, they were not categorized as serious and were frequently related to the central nervous system. However, study authors noted that larger trials of longer duration were needed to replicate or confirm the results, given the limited durations of active treatment and limited numbers of included participants. No literature was identified that compared long-term and short-term use of nabilone in PTSD or other chronic conditions. As such, the durability of treatment efficacy remains uncertain and it is unclear if some adverse effects may improve over time with extended treatment.

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REFERENCES

1. Management of Post-Tramautic Stress Working Group. VA/DoD clinical practice guideline for management post of-traumatic stress [Internet]. Washington (DC): U.S. Department of Veterans Affairs, Department of Defense; 2010 Oct. [cited 2015 Oct 7]. Available from: http://www.healthquality.va.gov/guidelines/MH/ptsd/cpgPTSDFULL201011612c.pdf

2. Van AM, Mancini C, Patterson B, Boyle MH. Post-traumatic stress disorder in Canada. CNS Neurosci Ther. 2008;14(3):171-81.

3. Ben AM. Cannabinoids in medicine: a review of their therapeutic potential. J Ethnopharmacol. 2006 Apr 21;105(1-2):1-25.

4. Cesamet® (nabilone): capsules; 1 mg, 05 mg, 0.25 mg [product monograph] [Internet]. Montreal (QC): Valeant Canada limitée/Limited; 2009 Mar 17. [cited 2015 Oct 7]. Available from: http://shoppers-healthcare-portal-a88a1f4b.s3.amazonaws.com/AgilityUGC/aee9130d-2bb3-4399-8284-1685c0d40c17/Cesamet_PM00007760_EN.PDF

5. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. J Clin Psychopharmacol [Internet]. 2014 Oct [cited 2015 Sep 22];34(5):559-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4165471

6. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol [Internet]. 2011 Nov [cited 2015 Sep 22];72(5):735-44. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243008

7. Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59.

8. 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 2015 Oct 15];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

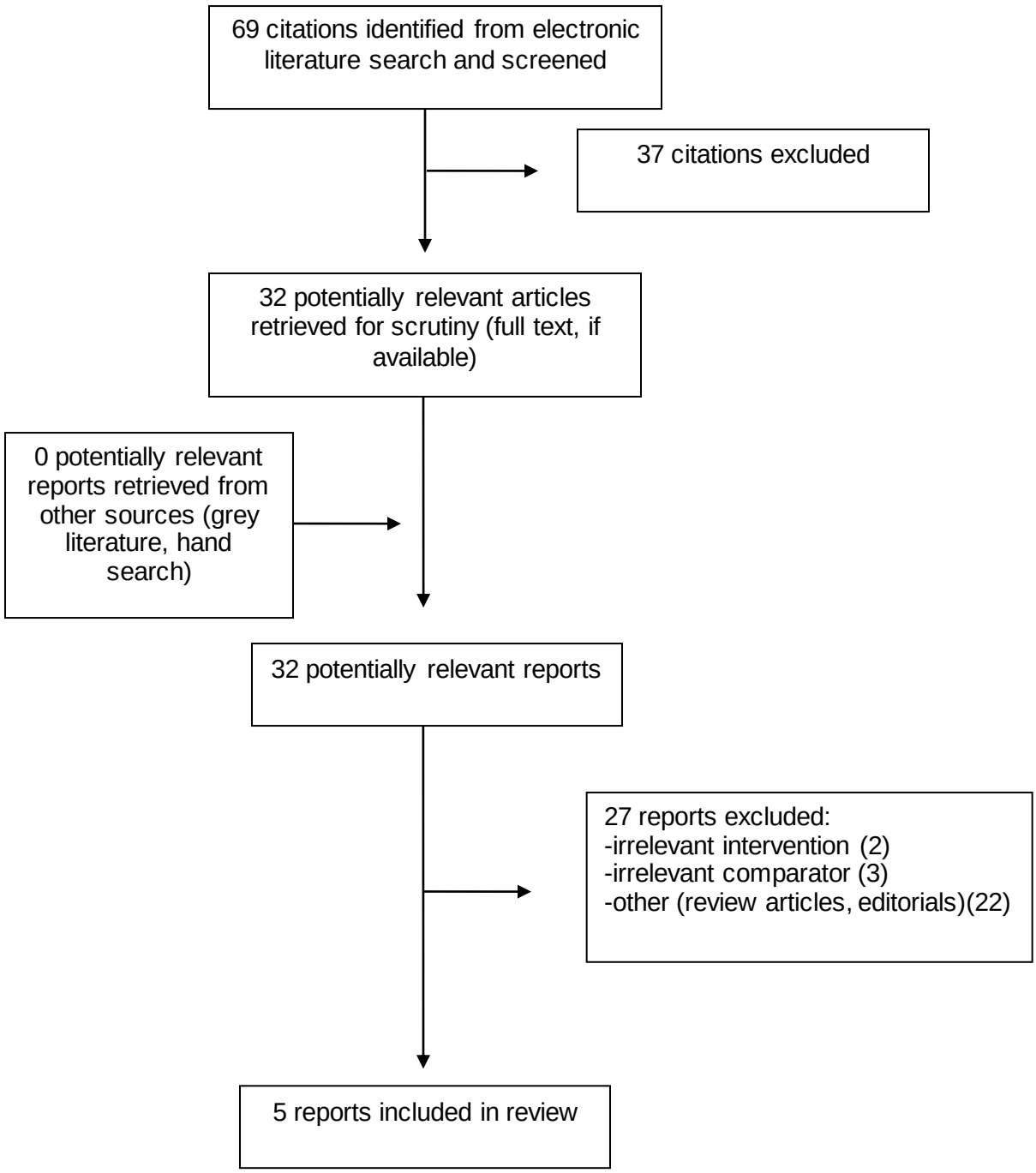
9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2015 Oct 15];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

10. Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology. 2015 Jan;51:585-8.

11. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82.

12. Pooyania S, Ethans K, Szturm T, Casey A, Perry D. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Arch Phys Med Rehabil. 2010 May;91(5):703-7.

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
Lynch 2011,[6] Canada	18 RCTs, 3 of which compared nabilone to placebo	40 patients with fibromyalgia – 1 RCT 13 patients with spasticity related pain – 1 crossover RCT 30 patients with chronic pain – 1 crossover RCT	Nabilone 0.25mg to 2.0mg daily	Placebo	Pain, adverse effects 4 weeks of treatment

RCT = Randomized controlled trial

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Randomized Controlled Trials					
Jetly 2015,[10] Canada	Randomized, double-blind, placebo-controlled cross-over design Randomized to either: Period 1 Nabilone/Period 2 Placebo Period 1 Placebo/Period 2 Nabilone 2 week washout between periods	10 male Canadian military personal (18 to 65 years) with PTSD and trauma-related nightmares. Mean (SD) Age: 43.6 (8.2)	Nabilone 0.5mg to 3.0mg daily for 7 weeks Titrated to effect and tolerability over 5 weeks, with dosage maintained for the final 2 weeks.	Placebo for 7 weeks.	CAPS Recurring and Distressing Dream Scores CGI-C WBQ Adverse effects

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Turcotte 2015,[7] Canada	Randomized, double-blind, placebo-controlled study	15 adult patients with inadequate control of MS-induced neuropathic pain, on stable dosages of gabapentin. Mean (SD) age: 45.5 (10.84) 87% female	Nabilone 1 mg twice daily for 9 weeks. Titrated up to 1mg twice daily over a 4 week period.	Placebo twice daily for 9 weeks.	VAS pain and impact scores recorded in a daily pain diary. CGI-C Adverse effects
Toth 2012,[11] Canada	Enriched-enrolment, randomized withdrawal, double-blind, placebo controlled trial Single-blind 4 week flexible dose of nabilone, followed by randomization to the same dosage achieved in the single-blind phase or to placebo	26 patients with diabetic peripheral neuropathic pain. Mean (SD) age: Nabilone: 60.8 (15.3) Placebo 61.6 (14.6) % Female Nabilone: 62% Placebo: 31%	Randomized phase Nabilone 1 mg to 4 mg per day for 5 weeks.	Placebo for 5 weeks.	Difference in average daily pain score (MBPI) Difference in average daily sleep disturbance score HADS EQ-5D MOSSS Adverse effects
Pooyania 2010,[12] Canada	Randomized, double-blind, placebo-controlled crossover study Randomized to either Period 1 Nabilone/Period 2 Placebo	12 male patients with spinal cord injury and spasticity Mean age: 42.4 (SD not reported)	Nabilone 0.5mg once to twice daily for 4 weeks	Placebo for 4 weeks.	Ashworth scale for spasticity Spasm frequency scale VAS CGI-C

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
	Period 1 Placebo/Period 2 Nabilone 2 week washout between periods				

CAPS=Clinician-Administered PTSD Scale; CGI=Clinical Global Impression of Change; EQ-5D=European Quality of Life Five dimensions; HADS=Hospital Anxiety and Depression Scale; MBPI: Modified Brief Pain Inventory; MOSSS=Medical Outcomes Study Sleep Scale; PTSD= Post-traumatic stress disorder; PTSS=Pain Treatment Satisfaction Scale; RCT = randomized controlled trial; SD=Standard deviation; VAS= Visual analog scale; WBQ= Well-Being Questionnaire

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR Checklist[8]

Strengths	Limitations
Lynch 2011[6]	
• Database search used to identify included studies, with a detailed search strategy provided. • Assessed study quality using a modified seven point, four item Oxford scale • Described the study outcome narratively, which appeared to be appropriate given the different indications included in the review. • Detailed characteristics of the included studies and their populations were provided. • The quality of the included studies was considered in formulating conclusions. • Conflict of interest was declared, with no competing interests noted.	• Unclear if an a priori design was used. • Study selection was performed by one individual. • It did not appear that publication bias was assessed. • A list of excluded studies was not provided.

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[9]

Strengths	Limitations
Jetly 2015,[10]	
Reporting • The objective of the study was clearly described. • The main outcomes were clearly described. • The intervention was clearly described and involved a dosage titration, which may be more reflective of real-world practice than a fixed dose. • Interventions of interest clearly stated. • Main study findings were clearly described. • The study provided estimates of the random variability in the data for the main outcomes and reported both means and medians. Internal Validity – Bias and Confounding • Both patients and outcome assessors were blinded, but it is unclear of the adverse effects of nabilone (such as sedation) could compromise the blinding. • Nonparametric tests were used for the statistical analysis, but it is unclear if a paired approach was taken. • The main outcome measures used appears to be reliable.	Reporting • Inclusion and exclusion criteria given, but the demographic and clinical characteristics of those included were not described, other than the average age. • The distributions of principal confounders in each group of subjects to be compared were not clearly described. • The reporting of adverse events was brief and limited in scope. • The characteristics of those patients with missing data were not reported. External Validity • The study sample included only 10 individuals. It is not clear of these individuals would be representative of the larger population. • Excluded patients who screened positive for illicit substances. • It is unclear if co-interventions were given and if the treatment received would be representative.

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[9]

Strengths	Limitations
External Validity • Study was conducted in Canada, which may make the results more generalizable to the Canadian practice than studies conducted outside of Canada.	Internal Validity – Bias and Confounding • Compliance with the study medication was not reported. • The method of randomization and allocation concealment was unclear. • The analysis was not a true intention to treat analysis and the loss to follow-up were not taken into account. Power • There was no power calculation performed.
Turcotte 2015,[7]	
Reporting • The objective of the study was clearly described. • The main outcomes were clearly described. • The intervention was clearly described and involved a dosage titration, which may be more reflective of real-world practice than a fixed dose. • Interventions of interest clearly stated. • The characteristics of those missing data were reported. Internal Validity – Bias and Confounding • Both patients and outcome assessors were blinded, but it is unclear of the adverse effects of nabilone (such as sedation) could compromise the blinding. • The main outcome measures used appears to be reliable. • The statistical modelling appeared to be appropriate. • Compliance with the study medication was not reported. External Validity • Study was conducted in Canada, which may make the results more generalizable to the Canadian practice than studies conducted outside of Canada. Power • The sample size was determined based upon a power calculation.	Reporting • Inclusion and exclusion criteria given, but the demographic and clinical characteristics of those included were not described, other than the average age. • The distributions of principal confounders in each group of subjects to be compared were not clearly described. • The reporting of adverse events was brief and limited in scope. • The main study findings were difficult to interpret with complex statistically modelling that was poorly explained. External Validity • The study sample included only 15 individuals. It is not clear of these individuals would be representative of the larger population. • Excluded patients with a history of substance abuse, emotional disorders. • Nabilone was given with gabapentin. It is unclear if the same result would be expected with nabilone alone. • Study was conducted in Canada, which may make the results more generalizable to the Canadian practice than studies conducted outside of Canada. Internal Validity – Bias and Confounding • The methods of randomization and allocation concealment were unclear. • The analysis was not a true intention to treat analysis and the loss to follow-up were not taken into account (assumed to be missing at random). • Compliance with the study medication was not reported.

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[9]

Strengths	Limitations
Toth 2012,[11]	
Reporting • The objective of the study was clearly described. • The main outcomes were clearly described. • The intervention was clearly described and involved a dosage titration, which may be more reflective of real-world practice than a fixed dose. • Interventions of interest clearly stated. • The characteristics of those missing data were not reported, but missing data were accounted for using MMRM and analyses were performed on an ITT population. • Inclusion and exclusion criteria given, with detailed demographic characteristics reported, which appeared balanced between groups. Internal Validity – Bias and Confounding • Both patients and outcome assessors were blinded, but it is unclear of the adverse effects of nabilone (such as sedation, dizziness) could compromise the blinding. • The main outcome measures used appears to be reliable. • The statistical modelling appeared to be appropriate. • Other medications (with the exception of cannabinoids) were permitted. It was unclear if use of other therapies was similar between groups. External Validity • Study was conducted in Canada, which may make the results more generalizable to the Canadian practice than studies conducted outside of Canada. Power • The sample size was determined based upon a power calculation.	Reporting • The reporting of adverse events was brief and limited in scope. • Exact p-values were not reported. Internal Validity – Bias and Confounding • Compliance with the study medication was not reported. • The authors expressed concern about carryover effects from the initial single-blind phase. External Validity • The study sample included only 26 individuals. It is not clear of these individuals would be representative of the larger population. • The exclusion criteria were extensive, which could limit the generalizability of the findings. • An enrichment design was used, and individuals who did not achieve a 30% pain reduction in the single blind phase were not randomized.
Pooyania 2010[12]	
Reporting • The objective of the study was clearly described. • The main outcomes were clearly described and were measured using standardized scales.	Reporting • The study population was not well-described, with very limited details of clinical and demographic characteristics.

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[9]

Strengths	Limitations
• The intervention was clearly described and involved a dosage titration, which may be more reflective of real-world practice than a fixed dose. • The main outcomes were well described and measured with standard scales. • Adverse effect data were reported with detail. • One patient dropped out, the details of which were clearly reported. • Exact p-values were reported. External Validity • Study was conducted in Canada, which may make the results more generalizable to the Canadian practice than studies conducted outside of Canada. Internal Validity – Bias and Confounding • Both patients and outcome assessors were blinded, but it is unclear of the adverse effects of nabilone (such as sedation) could compromise the blinding. • The main outcome measures used appears to be reliable. • The statistical modelling appeared to be appropriate.	Internal Validity – Bias and Confounding • The method of allocation concealment was unclear. • Compliance with the study medication was not reported. External Validity • The study sample included only 12 individuals. It is not clear of these individuals would be representative of the larger population. Power • There was no power calculation performed.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusions
Lynch 2011[6]	

Fibromyalgia (Nabilone versus Placebo)
• Efficacy
  ○ Significant decrease in 10 cm VAS pain (-2.04, P < 0.02)
  ○ Total FIQ (-12.07, P < 0.02)
  ○ 10 point FIQ anxiety (-1.67, P < 0.02)
• Adverse Effects
  ○ Dizziness
  ○ Disorientation
  ○ Nausea
  ○ Poor co-ordination
  ○ Drowsiness
  ○ Dry mouth
  ○ Vertigo
  ○ Ataxia
  ○ Headache
 	
Spasticity related pain (Nabilone versus Placebo)
• Efficacy
  ○ Significant decrease in spasticity related pain
  ○ No significant change in Ashworth scale or ADLs
• Adverse Effects
  ○ Drowsiness
  ○ Slight weakness legs
 	
Chronic pain
• Efficacy
  ○ Significant decrease in spinal pain intensity
• Adverse Effects
  ○ Fatigue
  ○ Dry mouth
  ○ Dizziness
	• *"cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain. Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large scale trials of longer duration reporting on pain and level of function are required".(p.742)*
	
	No conclusions were made specific to the use of nabilone for non-cancer related pain.

ADL=Activity of daily living; FIQ=Functional Impairment Questionnaire; VAS=Visual analog scale

Table A6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Jetly 2015[10]	
CAPS (Mean ± SD) Nabilone -3.6 ± 2.4 Placebo -1.0 ± 2.1 P = 0.03	• *"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*

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
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 **Treatment-related Adverse Effects** Nabilone 50% Placebo 60% Most common adverse effects with nabilone were dry mouth and headache.	*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*
Turcotte 2015[7]	
Pain Daily average VAS_{pain} scores indicated that the rate of loss of intensity was, on average, greater with nabilone than placebo. During the final 10 days of the trial, average VAS_{pain} scores were lower with nabilone than with placebo (P < 0.001), but not for VAS_{impact} (no data reported). **Improvement in PGIC** Nabilone 100% Placebo 43% P < 0.05 **Most Common Adverse Effects with Nabilone** Drowsiness – 63% Dry mouth – 50%	• *"Our results indicate that nabilone as an adjunctive to gabapentin is an effective, well-tolerated treatment option for pain management in this population."(p.157)*
Toth 2012[11]	
Mean difference in average daily pain score, week 5 – Nabilone more effective in improving pain than placebo (data not reported; P < 0.05) **Mean difference in sleep disturbance, week 5** – Nabilone less sleep disturbance than placebo (data not reported; P < 0.05) **HADS Anxiety** – Mean ± SD Nabilone: 5.0 ± 0.7 Placebo: 7.9 ± 1.4; P < 0.05	• *"…nabilone is an effective drug in management of neuropathic pain and associated promotion of sleep and quality of life in patients with neuropathic pain due to diabetic neuropathy." (p. 2081)*

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
HADS Depression – Mean ± SD Nabilone: 5.2 ± 0.9 Placebo: 5.6 ± 1.2 **EQ-5D Index** – Mean ± SD Nabilone: 0.74 ± 0.03 Placebo: 0.60 ± 0.08; P < 0.05 **MOSSS** – Mean ± SD Nabilone: 27.1 ± 2.1 Placebo: 33.0 ± 2.6; P < 0.05 **Adverse effects** *Single-Blind Phase:* Dizziness, dry mouth, drowsiness, confusion or impaired memory, lethargy, euphoria, headache, and increased appetite (frequency not reported). *Randomized, double-blind phase*: Treatment emergent adverse effects Nabilone – 54% Placebo – 46%	
Pooyania 2010[12]	
Mean difference between nabilone and placebo • Ashworth Scale for Spasticity In most involved muscle group: 0.91 ± 0.85; P = 0.003 Ashworth in 8 muscle groups: 2.55 ± 0.25; P = 0.001 • Spasm frequency scale 0 ± 0.193; P = 0.369 • VAS 9.09 ± 17; P = 0.076 • CGI-C 0.18 ± 1.16; P = 0.789 **Adverse Effects** Drowsiness, dry mouth, asthenia, mild vertigo, mild ataxia, headache, and lack of motivation	• *This randomized, double-blind, placebo-controlled study suggests that an orally administered cannabinoid, nabilone, may be beneficial to improve spasticity. The numbers in this study are small, and we recommend a larger trial with a more prolonged treatment period and an option to continue to slowly increase dosages.(p.707)*

CAPS=Clinician-Administered PTSD Scale; CGI=Clinical Global Impression of Change; EQ-5D=European quality of life five dimensions; HADS=Hospital Anxiety and Depression Scale; MOSSS=Medical outcomes study sleep scale; PTSD= Post-traumatic stress disorder; RCT = Randomized controlled trial; VAS= Visual analog scale; WBQ= Well-Being