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Nabilone for Chronic Pain Management: A Review of Clinical Effectiveness and Guidelines

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Context and Policy Issues

People with diseases that were once considered generally fatal, such as cancer and HIV/AIDS, are now surviving their acute illness with an increased quantity of life.[1] However, in many cases, a poor quality of life (QoL) ensues due to chronic pain caused by persisting illness, ongoing treatment, or lasting damage after resolution or cure of the disease.[1] Chronic pain, also caused by many other conditions, such as fibromyalgia, multiple sclerosis (MS), and neuropathy,[2] is difficult to treat,[3] a major contributor to time away from work,[3] and associated with increased risk of suicide.[1]

Cannabis and cannabis derivatives have been used since ancient times as an analgesic to relieve pain from a variety of conditions.[2,4] Cannabinoids are a relatively-new drug class derived from the active component delta-tetrahydrocannabinol of the plant *Cannabis sativa*.[5] Nabilone (Cesamet®) is a synthetic cannabinoid that mimics the action of delta-tetrahydrocannabinol[2] and has been approved by the US Food and Drug Administration[6] and Health Canada[7] to be used for the treatment of nausea and vomiting induced by chemotherapy.[5] Of particular interest is the off-label use of nabilone for pain, which is already employed as such in some settings.[7]

The purpose of this review is to provide evidence on the clinical benefits and harms and evidence-based guidelines on the use of nabilone in the management of chronic pain. This report is an update of a CADTH rapid response report published in 2011.[8]

Research Questions

1. What is the clinical effectiveness of nabilone for the treatment of chronic pain due to any disease in adults?
2. What are the evidence-based guidelines associated with the treatment of chronic pain due to any disease in adults?

Key Findings

One systematic review and two primary studies, all conducted in Canada, were identified. While there was evidence of some positive benefits and limited harms of nabilone, compared to placebo or known analgesics, in patients with cancer or non-cancer pain, the included literature had several limitations. The findings, therefore, should be interpreted with caution. No evidence-based guidelines provided recommendations on the use of nabilone for chronic pain management.

Methods

Literature Search Methods

A limited literature search was conducted on key resources, including Embase, Medline, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies. A focused Internet search was also conducted. 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, 2011 and July 17, 2017.

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 chronic pain due to any disease
Intervention	Nabilone (Cesamet®)
Comparator	Q1: Active treatments, placebo, or no treatment Q2: No comparator
Outcomes	Q1: Clinical effectiveness and clinical benefits (e.g., reduction in pain, pain relief, and patient satisfaction) and safety (e.g., harms, adverse events, and abuse and misuse) Q2: Guidelines
Study Designs	HTAs, SRs, MAs, RCTs, non-randomized primary studies, and evidence-based guidelines

HTA = health technology assessment; MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, if they were already included in the 2011 CADTH rapid response report, if they were reviews superseded or studies already included by at least one of the systematic reviews (SRs) selected in this report or the 2011 report, or if they were published prior to 2011.

Critical Appraisal of Individual Studies

The included SR and primary studies were assessed, using the Assessment of Multiple Systematic Reviews (AMSTAR) tool[9] and Downs and Black checklist.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was narratively described.

Summary of Evidence

Quantity of Research Available

A total of 91 citations were identified in the literature search. Following screening of titles and abstracts, 64 citations were excluded, and 27 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 the 31 potentially-relevant articles, 28 publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

A summary of the characteristics of the included literature is presented in Appendix 2.

Clinical Benefits and Harms of Nabilone for Chronic Pain Management

One SR[6] and two primary studies[5,7] provided information on the clinical effectiveness and safety of nabilone for chronic pain management.

Study Design

The SR[6] included four randomized controlled trials (RCTs) relevant to this report, published between 2010 and 2014.

One of the primary studies[5] was a double-blind RCT, and was published in 2016. The other primary study[7] was a single-intervention pre-and-post study, based on a retrospective chart review, and was published in 2014.

Country of Origin

The SR[6] and the primary studies[5,7] were conducted in Canada.

Patient Population

The SR[6] included 103 adults (sex/gender and age not reported) with chronic pain from any non-cancer condition, including fibromyalgia, medication-overuse headaches, MS, or diabetic neuropathy.

One of the primary studies[5] included 56 adults (82% male and 64 years of mean age) with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer. The other primary study[7] included 104 inmate adults (100% male and 33 years of mean age) with serious mental illness, including alcohol or substance abuse, anxiety, and post-traumatic stress disorder (PTSD), 68 of who had chronic neuropathic, musculoskeletal, or other pain.

Interventions and Comparators

The SR[6] compared nabilone with placebo or known analgesics, including amitriptyline (for fibromyalgia) and ibuprofen (for medication-overuse headaches), at unknown doses. Patients with MS were also on gabapentin.

One of the primary studies[5] compared nabilone, administered at a dose ranging from 0.5 mg/day to 2 mg/day, with placebo, during radiotherapy and/or chemotherapy treatment. The other primary study[7] compared before and after treatment with nabilone at a mean dose of 4 mg/day or a dose ranging from 0.5 mg/day to 6.0 mg/day.

Outcomes

The SR[6] described pain (measured with Brief Pain Inventory [BPI], McGill Pain Scale [MPS], Numeric Rating Scale [NRS], Patient Global Impression of Change [PGIC], or visual analogue scale [VAS]), anxiety (measured with Hospital Anxiety and Depression Scale [HADS]), sleep (measured with Insomnia Severity Index [ISI], Leeds Sleep Evaluation Questionnaire [LSEQ], or Medical Outcomes Study Sleep Scale [MOSSS]), analgesic intake (measured with Daily Analgesic Intake [DAI]), dependence level (measured with Leeds Dependence Questionnaire [LDQ]), and adverse events.

One of the primary studies[5] described pain (measured with VAS), appetite, body weight, nausea, mood, sleep, analgesic intake, QoL (measured with European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]), and adverse events. The other primary study[7] described pain (reported qualitatively by study participants).

Follow-Up Duration

The SR[6] included studies that ranged from two weeks to nine weeks in follow-up duration.

One of the primary studies[5] ranged from nine to 11 weeks in follow-up duration. The other primary study[7] reported a mean of 11.2 weeks and a range of one day to 36 weeks of follow-up duration.

Evidence-Based Guidelines for the Use of Nabilone for Chronic Pain Management

No evidence-based guidelines that provided recommendations on the use of nabilone for chronic pain management were identified.

Summary of Critical Appraisal

A summary of the critical appraisal of the included literature is presented in Appendix 3.

Clinical Benefits and Harms of Nabilone for Chronic Pain Management

The SR[6] was of mixed quality, based on the assessment made using the AMSTAR tool.[9] The authors performed a comprehensive literature search, including grey literature; provided a flow diagram for the literature search results and a list of the included studies and their characteristics; assessed the quality of the included studies and incorporated it in formulating conclusions; and used appropriate methods to summarize the findings of studies. However, there was no “a priori” design, no duplicate study selection or duplicate data extraction, no detailed literature search strategy, no list of the excluded studies, and no assessment of the likelihood of publication bias. Further, the authors declared conflicts of interest related to involvements with pharmaceutical companies and the Canadian Consortium for the Investigation of Cannabinoids.

One of the primary studies[5] was an RCT, which was generally well-conducted but had some limitations, based on the assessment made using the Downs and Black checklist.[10] The authors described the objective, interventions, and main outcomes of the study, the characteristics of the study participants and distributions of potential confounders in each intervention group, and the main findings and important adverse events, with estimates of the random variability in the data, using actual probability values. The authors made attempts to blind both the study participants and the staff, used accurate outcome measures and appropriate statistical tests, and had reliable compliance. As well, the authors recruited the study participants in different intervention groups from the same population over the same period of time, randomized them, and adjusted for confounding in the analysis. However, it was unclear whether the study participants were representative of the entire population of interest and whether the trial design was representative of the care setting. Further, the study participants lost to follow-up were not described in detail. Due to dropouts, the study was unlikely to have had sufficient power to detect clinically-important effects.

The other primary study[7] was a single-intervention pre-and-post study, based on a retrospective chart review, and had many limitations inherent to that study design, based on

the assessment made using the Downs and Black checklist.[10] The authors described the objective, intervention, and main outcomes of the study, the characteristics of the study participants in the intervention group, and the main findings and important adverse events. Since the study was based on a retrospective chart review, the trial design was likely representative of the care setting. The study also had sufficient power to detect clinically-important effects. Nevertheless, it was unclear whether the study participants were representative of the entire population of interest. Since this was a pre-and-post study, based on a retrospective chart review, no attempts were made to blind the study participants or the staff, and there was one intervention group, with no randomization and no adjustment for confounding. It was also unclear whether compliance with the interventions was reliable. Further, the pain outcome measure was subjective (reported qualitatively by the study participants), estimates of the random variability in the data for the main outcomes were not always provided, and statistical tests were not always conducted. The characteristics of the study participants lost to follow-up were not described in detail.

Summary of Findings

A summary of the findings of the included literature is presented in Appendix 4.

Clinical Benefits and Harms of Nabilone for Chronic Pain Management

Pain

One SR[6] reported that in patients with pain from MS or diabetic neuropathy receiving nabilone (plus gabapentin for MS), there was a significantly-greater reduction in pain, compared to those receiving placebo (plus gabapentin for MS). The SR[6] also reported that: in patients with chronic pain from fibromyalgia, there were no significant differences in pain between nabilone and amitriptyline groups; but in patients with chronic pain from medication-overuse headaches receiving nabilone, there was a greater reduction in pain, compared to those receiving ibuprofen.

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in pain or the time required for a 20% increase of pain between nabilone and placebo groups during cancer treatment.

The other primary study[7] reported that inmate male patients with serious mental illness and chronic neuropathic, musculoskeletal, or other pain receiving nabilone reported a subject improvement in pain, generally one week to two weeks after treatment, compared to before treatment. The effect was maintained for the balance of the trial.

Anxiety

One SR[6] reported that in patients with chronic pain from diabetic neuropathy receiving nabilone, there was a significantly-greater improvement in anxiety, compared to those receiving placebo.

Appetite

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in appetites between nabilone and placebo groups during cancer treatment.

Body Weight

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in body weights between nabilone and placebo groups during cancer treatment.

Mood

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in moods between nabilone and placebo groups during cancer treatment.

Nausea

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in nausea or the consumption of anti-emetic medications between nabilone and placebo groups during cancer treatment.

Sleep

One SR[6] reported that in patients with chronic pain from diabetic neuropathy receiving nabilone, there was a significantly-greater improvement in sleep, compared to those receiving placebo. The SR[6] also reported that in patients with chronic pain from fibromyalgia receiving nabilone, there was a greater improvement in sleep, compared to those receiving amitriptyline.

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in sleep between nabilone and placebo groups during cancer treatment.

Analgesic Intake

One SR[6] reported that in patients with chronic pain from medication-overuse headaches receiving nabilone, there was a greater reduction in daily analgesic intake, compared to those receiving ibuprofen.

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in antalgic medications between nabilone and placebo groups during cancer treatment.

Dependence Level

One SR[6] reported that in patients with chronic pain from medication-overuse headaches receiving nabilone, there was a greater reduction in the level of dependence, compared to those receiving ibuprofen.

Quality of Life

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no

significant differences in QoL between nabilone and placebo groups during cancer treatment.

Adverse Events

One SR[6] reported that in patients with chronic pain from any non-cancer condition, including fibromyalgia, medication-overuse headaches, MS, or diabetic neuropathy, the most common adverse events included drowsiness and fatigue. Other adverse events included dizziness, dry mouth, nausea, and cognitive effects. The SR[6] reported that the adverse events were generally mild to moderate in severity, transient, and well-tolerated and that one patient with diabetic neuropathy was seen in the emergency room for an assessment of delirium, which resolved when the medication was discontinued.

One of the primary studies[5] reported that in cancer patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in adverse events, including drowsiness, anxiety, and xerostomia between nabilone and placebo groups. However, while 32% of the patients receiving nabilone dropped out, 54% of those receiving placebo dropped out.

Limitations

In addition to the numerous limitations of the included literature identified in the quality assessments, such as the retrospective single-intervention pre-and-post study design,[7] lack of power,[5] and potential conflicts of interest,[6] other important limitations exist. The SR[6] and one of the primary studies[7] did not provide (most of) the numerical data or statistical testing results. The SR[6] and the other primary study[5] also identified as limitations the small sample sizes (i.e., 15 to 56 participants per study) and modest effect sizes of its included studies[6] or negative findings from its study, where nearly half the study population dropped out, leaving the study without adequate statistical power.[5] Therefore, it is difficult to assess the statistical or clinical significance of the described effects of nabilone from the included literature.

One of the primary studies[5] did not specify that the pain from cancer treatment was chronic. Therefore, the findings of the study may not be specific to chronic pain.

The SR[6] did not report the sex/gender or age of the study participants. The two primary studies had 82% male[5] or 100% male[5] adults in their study populations. Therefore, the findings of the studies may not be generalizable to female patients.

The primary studies included in the SR[6] and the two primary studies[5,7] were all short-term studies, with two weeks to 36 weeks of follow-up. Therefore, long-term effects of nabilone are unclear.

As the authors of the included literature mentioned, there is a need for larger and longer prospective trials to confirm the clinical effectiveness and safety of nabilone in chronic pain management.

Conclusions and Implications for Decision- or Policy-Making

One SR and two primary studies, all conducted in Canada, were identified. There was evidence of some positive benefits (e.g., improvements in pain, anxiety, and sleep) and limited harms (i.e., drowsiness, fatigue, dizziness) of nabilone, compared to placebo or known analgesics (i.e., amitriptyline for fibromyalgia and ibuprofen for medication-overuse

headaches), in patients with cancer or non-cancer pain. Nevertheless, the included literature had several limitations, and its findings should be interpreted with caution. Larger and longer prospective trials are needed to confirm the clinical effectiveness and safety of nabilone in chronic pain management. No evidence-based guidelines that provided recommendations on the use of nabilone for chronic pain management were identified.

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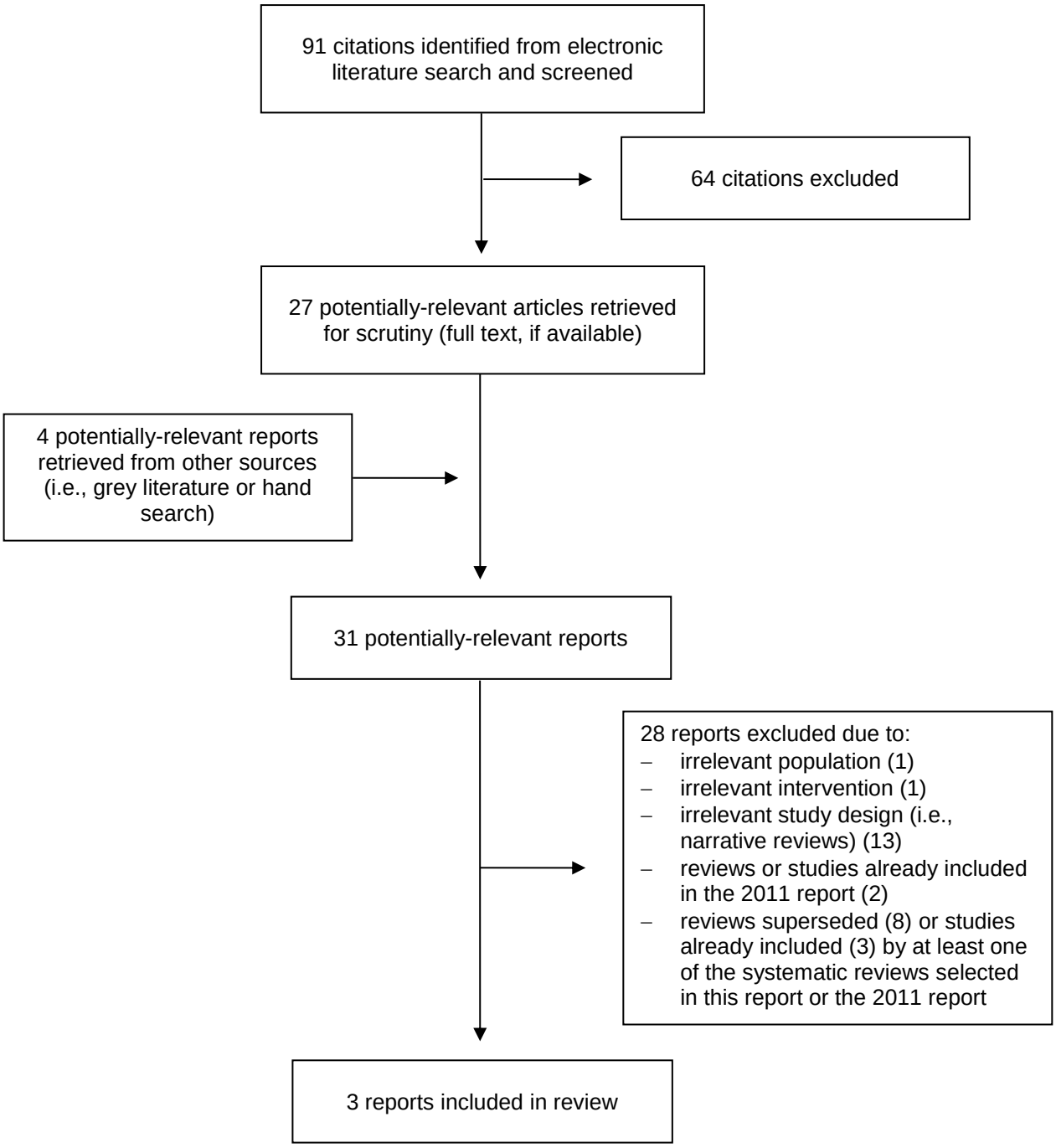
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Review

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included, Quality Assessment	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Lynch[6] 2015 Canada	SR of 4 RCTs*, published between 2010 and 2014 Quality assessment using modified Oxford Scale *Of the 11 RCTs on cannabinoids included in the SR, 4 RCTs were on nabilone.	103 adults* with chronic pain from any non-cancer condition, including fibromyalgia, medication-overuse headaches, MS, or diabetic neuropathy *Sex/gender=NR; age=NR	Nabilone*,** *Dose=NR **Patients with MS were also on gabapentin.	Placebo* or known analgesics, including amitriptyline** and ibuprofen** *Patients with MS were also on gabapentin. **Dose=NR	Pain*, anxiety**, sleep***, analgesic intake****, dependence level*****, and AEs 2-9 weeks of follow-up *Assessed using BPI, MPS, NRS, PGIC, or VAS **Assessed using HADS ***Assessed using ISI, LSEQ, or MOSSS ****Assessed using DAI *****Assessed using LDQ

AE = adverse event; BPI = Brief Pain Inventory; DAI = Daily Analgesic Intake; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; LDQ = Leeds Dependence Questionnaire; LSEQ = Leeds Sleep Evaluation Questionnaire; MOSSS = Medical Outcomes Study Sleep Scale; MPS = McGill Pain Scale; MS = multiple sclerosis; NR = not reported; NRS = Numeric Rating Scale; PGIC = Patient Global Impression of Change; RCT = randomized controlled trial; SR = systematic review; VAS = visual analogue scale.

Table A2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Cote[5] 2016 Canada	Double-blind RCT	56 adults* with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer *82% male; mean 64 years of age	Nabilone*, administered during radiotherapy and/or chemotherapy treatment *0.5-2 mg/day	Placebo, administered during radiotherapy and/or chemotherapy treatment	Pain*, appetite, body weight, nausea, mood, sleep, analgesic intake, QoL**, and AEs 9-11 weeks of follow-up *Assessed using VAS **Assessed using EORTC QLQ
Cameron[7] 2014 Canada	Single-intervention pre-and-post study, based on a retrospective chart review	104 inmate adults* with serious mental illness, including alcohol or substance abuse, anxiety, and PTSD, 68 of who had chronic neuropathic, musculoskeletal, or other pain *100% male; mean 33 years of age (range: 19-55 years)	Nabilone*, administered in power form with water to minimize risk of abuse or diversion *Mean 4 mg/day (range: 0.5-6.0 mg/day)	Pre-treatment	Pain*,** Mean 11.2 weeks of follow-up (range: 1 day-36 weeks) *Reported qualitatively by the study participants **While other outcomes were also reported, they were not specific to the 68 patients with chronic pain.

AE = adverse event; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PTSD = post-traumatic stress disorder; QoL = quality of life; RCT = randomized controlled trial; VAS = visual analogue scale.

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Included Systematic Review Using AMSTAR

Strengths	Limitations
Lynch 2015[6]	
• A comprehensive literature search, including grey literature, was performed. • A flow diagram for the literature search results was provided. • A list of the included studies was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented, and the included studies were rated on their quality. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to qualitatively summarize the findings of studies, which varied in diseases, comparators, and follow-up durations, were appropriate.	• An "a priori" design was not provided. • There was no duplicate study selection or duplicate data extraction. • A detailed literature search strategy was not provided. • A list of the excluded studies was not provided. • The likelihood of publication bias was not assessed. • Both authors declared conflicts of interest related to involvements with pharmaceutical companies and the Canadian Consortium for the Investigation of Cannabinoids.

AMSTAR = Assessment of Multiple Systematic Reviews.

Table A4: Strengths and Limitations of Included Primary Studies Using Downs and Black

Strengths	Limitations	Irrelevant Items
Cote 2016[5]		
<u>Reporting</u> • The objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study participants were described. • The interventions were described. • The distributions of potential confounders in each intervention group of the study participants were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Important adverse events were reported. • Actual probability values were reported. <u>Bias</u> • An attempt was made to blind the study participants to the intervention they received. • An attempt was made to blind the staff measuring the main outcomes. • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable.	<u>Reporting</u> • The characteristics of the study participants lost to follow-up were not described in detail. <u>External Validity</u> • It is unclear whether the individuals asked to participate in the study were representative of the entire population of interest. • It is unclear whether the study participants were representative of the entire population of interest. • The trial design may not be representative of the care setting. <u>Confounding</u> • Losses of study participants to follow-up were not taken into account. <u>Power</u> • Due to dropouts, the study was unlikely to have had sufficient power to detect clinically-important effects.	<u>Bias</u> • No post hoc analyses were described.

Strengths	Limitations	Irrelevant Items
• The main outcome measures were accurate (i.e., valid and reliable). Confounding • The study participants in different intervention groups were recruited from the same population over the same period of time. • The study participants were randomized to intervention groups. • Intervention assignment was concealed from both study participants and staff until recruitment was complete and irrevocable. • There was adequate adjustment for confounding in the analysis for the main findings.		
Cameron 2014[7]		
Reporting • The objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study participants were described. • The intervention was described. • The main findings were described. • Important adverse events were reported. • Where reported, actual probability values were provided. External Validity • Since the study was based on a retrospective chart review, the trial design was likely representative of the care setting. Power • The study had sufficient power to detect clinically-important effects.	Reporting • Since this was a pre-and-post study, distributions of potential confounders in the intervention group of the study participants could not be described. • Estimates of the random variability in the data for the main outcomes were not always provided. • The characteristics of the study participants lost to follow-up were not described in detail. External Validity • It is unclear whether the individuals asked to participate in the study were representative of the entire population of interest. • It is unclear whether the study participants were representative of the entire population of interest. Bias • Since the study was based on a retrospective chart review, no attempt was made to blind the study participants to the intervention they received. • Since the study was based on a retrospective chart review, no attempt was made to blind the staff measuring the main outcomes. • Statistical tests were not always conducted to assess the main outcomes. • It is unclear whether compliance with the interventions was reliable. • The pain outcome measure was subjective. Confounding • Since this was a pre-and-post study, there was only one intervention group. • The study participants were not randomized to intervention and control groups. • There was no intervention assignment concealment from either study participants or staff. • There was no adjustment for confounding in the analysis for the main findings. • Losses of study participants to follow-up were not taken into account.	Bias • No post hoc analyses were described.

Appendix 4: Main Study Findings and Authors' Conclusions

Table A5: Summary of Findings of Included Systematic Review

Main Study Findings	Authors' Conclusions
Lynch 2015[6]	

Pain
• (2 studies) In patients with chronic pain from MS or diabetic neuropathy receiving nabilone (+gabapentin for MS), there was a significantly-greater reduction in pain, compared to those receiving placebo (+gabapentin for MS).
  ○ (1 study; 7/7 on Oxford quality scale) MS: data=NR
  ○ (1 study; 7/7 on Oxford quality scale) diabetic neuropathy: ≥30% reduction in pain 85% (11/13) vs 38% (5/13), *P*=NR
• (1 study; 7/7 on Oxford quality scale) In patients with chronic pain from fibromyalgia, there were no significant differences in pain between nabilone and amitriptyline groups (data=NR).
• (1 study; 6/7 on Oxford quality scale) In patients with chronic pain from medication-overuse headaches receiving nabilone, there was a greater reduction in pain, compared to those receiving ibuprofen (data=NR).
Anxiety
• (1 studies; 7/7 on Oxford quality scale) In patients with chronic pain from diabetic neuropathy receiving nabilone, there was a significantly-greater improvement in anxiety, compared to those receiving placebo (data=NR).
Sleep
• (1 studies; 7/7 on Oxford quality scale) In patients with chronic pain from diabetic neuropathy receiving nabilone, there was a significantly-greater improvement in sleep, compared to those receiving placebo (data=NR).
• (1 study; 7/7 on Oxford quality scale) In patients with chronic pain from fibromyalgia receiving nabilone, there was a greater improvement in sleep, compared to those receiving amitriptyline (data=NR).
Analgesic Intake
• (1 study; 6/7 on Oxford quality scale) In patients with chronic pain from medication-overuse headaches receiving nabilone, there was a greater reduction in daily analgesic intake, compared to those receiving ibuprofen (data=NR).
Dependence Level
• (1 study; 6/7 on Oxford quality scale) In patients with chronic pain from medication-overuse headaches receiving nabilone, there was a greater reduction in the level of dependence, compared to those receiving ibuprofen (data=NR).
Adverse Events
• The most common AEs included drowsiness and fatigue. Other AEs included dizziness, dry mouth, nausea, and cognitive effects.
• The AEs were generally mild to moderate in severity, transient, and well-tolerated. One patient with diabetic neuropathy was seen in the emergency room for an assessment of delirium, which resolved when the medication was discontinued.
	• Currently-available cannabinoids are safe, modestly-effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain. The quality of the trials was excellent.
	• There is a need for larger and longer trials to confirm efficacy and safety considerations.

AE = adverse event; MS = multiple sclerosis; NR = not reported; vs = versus.

Table A6: Summary of Findings of Included Primary Studies

Main Study Findings	Authors' Conclusions
Cote 2016[5]	
Pain • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in pain (*P*=0.6048) or the time required for a 20% increase of pain (*P*=0.4614) between nabilone and placebo groups during cancer treatment. Appetite • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in appetites between nabilone and placebo groups (*P*=0.3295) during cancer treatment. Body Weight • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in body weights between nabilone and placebo groups (*P*=0.1454) during cancer treatment. Mood • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in moods between nabilone and placebo groups (*P*=0.3214) during cancer treatment. Nausea • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in nausea (*P*=0.7105) or the consumption of anti-emetic medications (*P*=0.6124) between nabilone and placebo groups during cancer treatment. Sleep • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in sleep between nabilone and placebo groups (*P*=0.4438) during cancer treatment. Analgesic Intake • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in the consumption of antalgic medications between nabilone and placebo groups (*P*=0.6671) during cancer treatment. Quality of Life • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in QoL between nabilone and placebo groups (*P*=0.4270) during cancer treatment. Adverse Events • In patients with pain from radiotherapy and/or chemotherapy treatment for head and neck cancer receiving nabilone, there were no significant differences in AEs, including drowsiness (*P*=0.3166), anxiety (*P*=0.9163), and xerostomia (*P*=0.8341), between nabilone and placebo groups. • While the patients receiving nabilone reported 20 other AEs, those receiving placebo reported 24 other AEs, mostly related to radiotherapy treatment (*P*=NR). • While 32% (9/28) of the patients receiving nabilone dropped out, 54% (15/28) of those receiving placebo dropped out (*P*=NR). Reasons	• At the dosage used, nabilone was not potent enough to improve patients' pain, nausea, QoL, or any other outcomes monitored during cancer treatment, compared to placebo. • Nabilone has limited toxicity and is well-tolerated by patients receiving cancer treatment.

Main Study Findings	Authors' Conclusions
included nausea (n=5), difficulty swallowing the medications (n=4), hospitalization (n=4), pneumonia (n=1), discontinued radiotherapy (n=1), or none provided (n=9).	
Cameron 2014[7]	
Pain • 89.6% (61/68) patients with chronic neuropathic, musculoskeletal, or other pain receiving nabilone reported a subject improvement in pain, generally 1-2 weeks after treatment, compared to before treatment (data=NR). The effect was maintained for the balance of the trial.	• This study supports the promise of nabilone as an effective treatment for pain in seriously-mentally-ill correctional populations. • Prospective RCTs are required to confirm the preliminary results. Follow-up in the community will be required to confirm effectiveness in harm reduction.

AE = adverse event; NR = not reported; QoL = quality of life; RCT = randomized controlled trial.

Appendix 5: Additional References of Potential Interest

Guidelines that are not direct or specific to, but may be inclusive of, nabilone:

- Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. CMAJ [Internet]. 2017 [cited 2017 Aug 8]; 189(18):E659-66. Available from: http://www.cmaj.ca/content/189/18/E659.

Non-evidence-based guidelines:

- Nabilone for the treatment of chronic non cancer pain (unlicensed indication). Manchester (UK): Greater Manchester Medicines Management Group (GMMMG); 2014 [cited 2017 Aug 8]. Available from: http://gmmmg.nhs.uk/docs/nts/NTS%20Recommendation%20for%20Nabilone%20in%20Chronic%20non%20cancer%20pain%20(unlicensed).pdf.