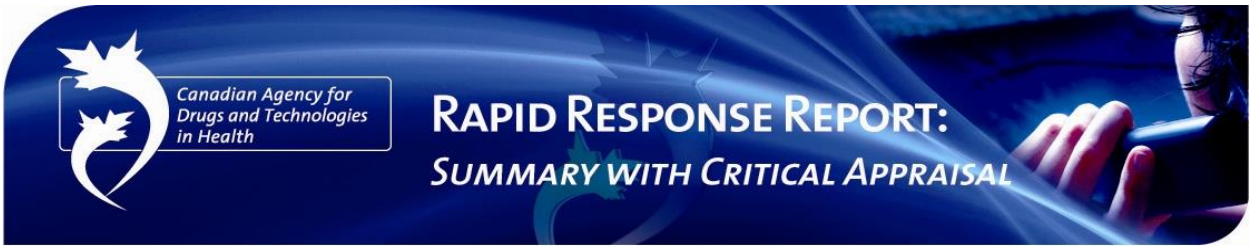


**TITLE: Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines**

**DATE:** 21 September 2016

## CONTEXT AND POLICY ISSUES

Chronic pain is a complex, severe and debilitating condition which can lead to a considerable reduction in function and quality of life.[1,2] Patients may present with different forms of chronic pain resulting from a number of identifiable causes, including pain due to lesion or dysfunction of the nerves, spinal cord or brain (neuropathic pain), or persistent pain caused by other non-malignant conditions, such as low-back pain or pain due to inflammation of various arthritic conditions.[3,4] The prevalence of chronic non-cancer pain or neuropathic pain among Canadian adults is not well known. However, prevalence estimates using large, population-based questionnaires have shown that 4% to 8% of the general population in the developed world experiences neuropathic pain, suggesting that approximately two million Canadians may be affected by this disabling condition.[5,6] Chronic pain is of particular concern among Canadians aged 65 years and older; based on cross-sectional data from the 1996/1997 National Population Health Survey and the 2005 Canadian Community Health Survey, chronic pain was estimated to affect 27% and 38% of seniors living in households and health care institutions, respectively.[7]

A number of treatments are available for the management of neuropathic pain or chronic non-cancer pain. These include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine), anticonvulsants (pregabalin, gabapentin, carbamazepine, phenytoin), topical lidocaine, and opioid analgesics.[8,9] However, these medications are associated with limited pain relief and numerous adverse effects.[8,9] The therapeutic use of several synthetic cannabinoid products for the symptomatic relief of chronic pain has also been studied.[10] In particular, a combination of two products, delta-9-tetrahydrocannabinol and cannabidiol (THC:CBD) marketed under the name Sativex® is available for use as a buccal spray.[10,11] This cannabis-based agent is approved for use in Canada as an add-on therapy for adult patients experiencing muscle spasticity caused by multiple sclerosis (MS), and it has received a Notice of Compliance with conditions for MS-related central neuropathic pain and the treatment of cancer pain unresponsive to opioids.[11]

The purpose of this review is to examine the available published literature relating to THC:CBD buccal spray for the treatment of chronic non-cancer or neuropathic pain in adults.

## RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of delta-9-tetrahydrocannabinol/cannabidiol for the treatment of adult patients with chronic non-cancer pain or neuropathic pain?

2. What are the evidence-based guidelines relating to the use of delta-9-tetrahydrocannabinol/cannabidiol for adult patients with chronic non-cancer pain or neuropathic pain?

## KEY FINDINGS

Five systematic reviews, including two with meta-analyses, were identified relating to the clinical effectiveness of delta-9-tetrahydrocannabinol/cannabidiol (THC:CBD) buccal spray for the treatment of chronic neuropathic or non-cancer pain. Based on the identified published literature, THC:CBD buccal spray may be associated with favourable short-term patient outcomes, including reduced levels of perceived pain and a good tolerability, when compared with placebo therapy. However, sustained benefit of short-term clinical outcomes and safety over a longer term is unclear, and the clinical effectiveness of THC:CBD oral spray in comparison with other pharmacologic treatments is currently lacking.

One evidence-based guideline was identified that recommends third-line use of THC:CBD buccal spray for patients uncontrolled on drug therapy in the management of chronic neuropathic pain.

## METHODS

### Literature Search Methods

A limited literature search was conducted on key resources including Embase via Ovid, MEDLINE via Ovid, 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. Conference abstracts were excluded from the search results. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and March 16, 2016.

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** | Adult patients with chronic non-cancer pain or neuropathic pain |
| **Intervention** | Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) |
| **Comparators** | • Nabilone<br>• Opioids<br>• Anti-convulsants<br>• Anti-depressants (e.g., tricyclic antidepressants, SSRIs, SNRIs)<br>• Placebo |
| **Outcomes** | Q1: Clinical benefits and harms (e.g. pain relief, safety)<br>Q2: Evidence-based guidelines |
| **Study Designs** | Health technology assessments, systematic reviews and/or meta-analyses, randomized controlled trials, evidence-based guidelines |

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or if they were published prior to 2010. Guidelines were excluded if they did not clearly indicate a formal literature search and/or assessment of the quality of the evidence upon which the recommendations were based.

### Critical Appraisal of Individual Studies

The scientific quality of included studies was carefully assessed based on their study design. Systematic reviews (SRs) and meta-analyses were critically appraised using the AMSTAR instrument,[12] while the methodological quality of evidence-based guidelines was assessed using the AGREE II tool.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was performed and described narratively.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

A total of 416 citations were identified in the literature search. Following screening of titles and abstracts, 385 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search, and an additional four records were identified through hand searching of reference lists. Of the 36 articles selected for full-text review, 30 articles were excluded for various reasons, and a total of six publications met the selection criteria for inclusion in this report. Appendix 1 presents the PRISMA flow diagram of the study selection process, including reasons for exclusion of full-text publications

Additional studies of potential interest that did not meet the selection criteria are provided in Appendix 6.

## Summary of Study Characteristics

A brief overview of the studies selected for inclusion can be found in Appendix 2.

*Study Design*

Five SRs,[2,14-16] including two with meta-analyses,[16,17] were identified regarding the clinical effectiveness of cannabinoids in the management of chronic pain among adults; all SRs evaluated the comparative clinical benefits and harms associated with THC:CBD (Sativex®) in adults experiencing chronic neuropathic or non-cancer pain. There was overlap among the placebo-controlled RCTs relating to THC:CBD in the five published SRs identified for inclusion (Appendix 3). Nine RCTs were common between at least two SRs, while seven RCTs were unique to a single SR. Variation between the studies selected for inclusion across these reviews likely occurred due to differences in the eligible patient populations, in chosen comparators and the search timeframes used; all SRs included data on randomized, placebo-controlled trials.

One evidence-based guideline met the inclusion criteria for this review.[18] This guideline was developed by means of expert consensus and systematic literature searches using an evidence grading approach developed by the American Academy of Neurology. Treatment recommendations were specific to the pharmacological management of chronic neuropathic pain in adult patients.

*Country of Origin*

Of the five included SRs, two were conducted in the United States,[14,17] and one review was conducted in the United Kingdom.[16] One SR was conducted in Canada,[2] and an updated review was subsequently published by the same primary author.[15]

The included evidence-based guideline statement was the product of collaboration between clinicians and researchers from Canada, endorsed by the Canadian Pain Society.[18]

*Patient Population*

All included SRs assessed the clinical benefits and safety of THC:CBD among patients with chronic pain. More specifically, patients with chronic neuropathic pain or chronic non-cancer pain related to fibromyalgia, rheumatoid arthritis, and mixed chronic pain were the focus of the SR published by Lynch et al.[2]; in their updated review, the authors defined the target population more broadly as patients with chronic non-cancer pain. Conversely, the review by Jawahar et al.[17] focused on patients clinically diagnosed with multiple sclerosis and experiencing non-spastic and non-trigeminal neuralgic pain, while Boychuk et al.[14] included studies relating to patients with chronic non-malignant neuropathic pain. The SR and meta-analysis by Whiting et al.,[16] which included the largest number of primary studies, assessed the effectiveness of cannabinoid products across a wide range of clinical areas, including chronic pain; studies relating to the effect of THC:CBD on chronic pain in this review included patients with cancer and non-cancer pain. None of the included SRs described patients' prior treatment experience with analgesic medications.

The intended users of the included evidence-based guideline were described as physicians, nurse practitioners and other allied health care professionals involved in the management of neuropathic pain; the guideline is also relevant to patients with chronic neuropathic pain.[18]

*Interventions and Comparators*

Cannabinoid products comprised the main interventions of interest across all included SRs. These products included whole plant cannabinoids such as smoked cannabis, cannabinoid extracts delivered as aerosol spray such as THC:CBD which was of particular interest in this report, as well as synthetic cannabinoids ingested orally such as nabilone or dronabinol. The effectiveness of THC:CBD in RCTs included across all SRs were exclusively compared with placebo. Studies comparing THC:CBD with other active comparators relevant to this review, such as nabilone, opioids, anticonvulsant or antidepressant medications, were not identified.

The included evidence-based guideline focused specifically on pharmacologic treatments for the management of chronic neuropathic pain, including cannabinoid products such as THC:CBD.

*Outcomes*

The primary clinical outcome across all SRs was patient-reported pain relief measured using validated pain scales (i.e. Numerical Rating Scale [NmRS],[2,14-17] Visual Analogue Scale [VAS],[2,16,17] Neuropathic Pain Scale [NPS],[2,14-16] Pain Disability Index [PDI],[2,14] Brief Pain Inventory [BPI],[15-17] and McGill Pain Questionnaire – Short Form [SF-MPQ][2]). The rate of adverse events, including serious adverse events, drug-related withdrawals, and frequently reported side effects, was the secondary outcome among all SRs. One SR also attempted to quantify patients' activities of daily living and quality of life,[16] and another SR measured patients' level of function as a secondary outcome measure.[2] The length of follow-up across studies included across all reviews spanned the period from one week to 15 weeks.

The included evidence-based guideline provided recommendations of the differential diagnosis of neuropathic pain, therapeutic options, and presented a clinical practice algorithm. The evidence for different pharmacological pain management options was rated using a grading system developed by the American Academy of Neurology (AAN).[18] Specific criteria were developed based on the type of clinical question (e.g. diagnostic, prognostic, therapeutic) and are used to guide the rating of published evidence into one of four categories based on methodological rigour (Class I to Class IV, with Class I representing the highest quality studies).

**Summary of Critical Appraisal**

A detailed overview of the strengths and limitations of each included study is presented in Appendix 4.

*Systematic Reviews*

The included SRs were generally well designed. Namely, all review authors utilized a comprehensive literature search across several electronic databases, and four out of five reviews enforced duplicate article screening and duplicate extraction of data with a consensus procedure in case of disagreements.[14-17] A list of included studies and individual study characteristics was provided by four review authors in tabular format,[2,15-17] while the authors of one review described the study characteristics narratively.[14] In addition, the methodological rigour and scientific quality of included studies was assessed across all reviews and were considered appropriately in the analysis and formulation of conclusions in four SRs.[2,14,16,17]

Despite the application of best practices in the conduct of SRs, there were also some concerns relating to these studies. Namely, while one SR clearly stated that the research questions posed and inclusion criteria used were established a priori and referenced a study protocol,[16] it was unclear whether the authors of four SRs[2,14,15,17] pre-defined the published research objectives or developed a review protocol in order to avoid bias in selecting studies during the review process. Furthermore, in three SRs where data were not statistically combined in a meta-analysis,[2,14,15] one of three reviews justified the decision to not statistically pool the results.[2] While the authors of one review calculated pooled effect sizes when data from three or more studies were available, the appropriateness of combining results based on consideration for between- and within-study variation (statistical and clinical heterogeneity) was not described.[17] Finally, while the review authors' potential conflicts of interest were clearly acknowledged in all SRs, sources of funding of included studies were not described in four of five reviews.[2,14-16] The likelihood of publication bias was not assessed in any of the included SRs.

*Guidelines*

Methodological quality of the included evidence-based guideline was evaluated using the AGREE-II instrument.[13] The quality of this guideline document is strengthened by the inclusion of a clear description of the objective and its intended users, the use of a systematic search in identifying published evidence to support recommendations, as well as consideration for health benefits, adverse effects, and risks in formulating recommendations, and guidance on how the recommendations can be put into practice. Nevertheless, reporting regarding the process of guideline development was unclear; namely, while a systematic search of the literature was conducted, the use of systematic methods in reviewing the published evidence was not clearly reported, and it was unclear whether stakeholder involvement considered the views and preferences of patient representatives. In addition, it was unclear whether the guideline was externally reviewed by experts prior to publication, and the guideline does not describe facilitators and barriers to its application. Finally, while the competing interests of the guideline authors were disclosed, it remains unclear whether the views of the funding body influenced the content of the guideline.

## Summary of Findings

*What is the clinical effectiveness and safety of delta-9-tetrahydrocannabinol/cannabidiol for the treatment of adult patients with chronic non-cancer pain or neuropathic pain?*

The clinical effectiveness and safety of THC:CBD (Sativex®) for the treatment of chronic neuropathic or non-cancer pain in adults is summarized below based on outcomes relating to patient-related benefits and harms, as reported by the original study authors. A detailed synthesis of the results of each included study is presented in Appendix 5.

Pain relief

Patient-reported pain relief following treatment with THC:CBD in comparison with placebo therapy was reported across all included reviews. In general, the review authors' conclusions regarding the direction and magnitude of the analgesic effect related to THC:CBD, as compared with placebo, are conflicting. Disagreements between the published reviews are summarized below.

In the SR by Lynch et al.[2] which evaluated the effect of THC:CBD against placebo in patients with chronic non-cancer pain, the authors reported that findings from five RCTs revealed a statistically significant reduction in pain on validated patient-reported pain measures (i.e. NmRS, VAS, NPS, PDI, SF-MPQ) when comparing THC:CBD with placebo; however, Lynch et al. also found evidence from two RCTs which did not support a statistically significant difference in pain scores between the active treatment and placebo. Nevertheless, the authors concluded that cannabinoids, including THC:CBD, are modestly effective in reducing pain among patients with chronic non-cancer pain. Furthermore, in their updated review,[15] Lynch et al. identified an additional two placebo-controlled RCTs concerning the effect of THC:CBD on chronic non-cancer pain. Despite the lack of a statistically significant reduction in pain observed at the last follow-up in a 14-week RCT cited by the review authors, it was suggested that the updated review adds further support to the available evidence showing that cannabinoids (including THC:CBD) are modestly effective analgesic products for the management of chronic non-cancer pain.

In contrast to the reviews by Lynch et al.,[2,15] Jawahar et al.[17] drew the conclusion that nabiximols, the main drug class to which THC:CBD belongs, are not effective agents for relieving chronic pain. However, this finding relates specifically to the management of multiple sclerosis patients who are experiencing non-spastic and non-trigeminal neuralgic pain, and the conclusion elicited in this review is based on a pooled effect size derived using data from three placebo-controlled RCTs which did not reach statistical significance for pain reduction.

In the SR by Boychuk et al.[14] which assessed the therapeutic effect of THC:CBD among patients with chronic non-malignant neuropathic pain, the authors identified three 3 placebo-controlled RCTs which found a statistically significant reduction in mean pain intensity following treatment with THC:CBD. However, the review authors also found evidence from two other placebo-controlled RCTs which found no significant difference in pain at the last follow-up between patients treated with THC:CBD and placebo. As a result, Boychuk et al. concluded that THC:CBD may provide an effective analgesic effect in chronic neuropathic pain conditions that are unresponsive to other treatments.

Whiting et al.[16] statistically combined the results from a number of placebo-controlled RCTs relating to the effect of THC:CBD in alleviating chronic pain resulting from malignant and non-malignant causes. While the authors found that the average number of patients reporting a 30% or greater reduction in pain was greater with cannabinoids (THC and THC:CBD), the results of the pooled analyses were not statistically significant. Given that the pooled analysis was conducted using one RCT evaluating the effectiveness of THC alone and two RCTs conducted among cancer patients in addition to five RCTs relating to the use of THC:CBD for non-cancer pain, the pooled analgesic effect of THC:CBD for non-cancer pain was not reported. The authors concluded that there was moderate quality evidence supporting the use of cannabinoids in the management of chronic pain.

Adverse events

The rate of adverse events following treatment with THC:CBD, as compared with placebo, was reported across all included SRs. Similarly to findings regarding the effect of THC:CBD in alleviating chronic neuropathic and non-cancer pain, evidence regarding the comparative safety of THC:CBD in patients experiencing chronic pain is not consistent across all included SRs. Inconsistencies in the published literature are summarized below.

Based on the SR and updated review by Lynch et al.,[2,15] the authors drew the conclusion that cannabinoids, and THC:CBD in particular, are a safe treatment option for chronic non-cancer (mainly neuropathic) pain. This conclusion was made on the basis of no serious (life-threatening) adverse events observed across all RCTs included in the initial SR,[2] and two serious adverse events noted in patients who received THC:CBD in one RCT identified in the updated review.[15] While the authors listed a number of common drug-related adverse events reported in the published RCTs, these adverse events were considered to be minor in nature and did not impact the authors' conclusions regarding the safety of THC:CBD. Similarly to the conclusions made by Lynch et al., Boychuk et al.[14] found that very few risks were associated with the use of cannabinoid products such as THC:CBD in the treatment of chronic neuropathic pain. The authors drew this conclusion based on a review of five placebo-controlled RCTs relating to THC:CBD, three of which suggested an increased incidence of mouth ulcers, dysgeusia (alteration in taste), and sore throat following use of THC:CBD oromucosal spray. Much like Lynch et al., Boychuk et al. did not consider the observed adverse event to be major.

In contrast to these SRs, Whiting et al.[16] combined data on adverse events in a meta-analysis and drew the conclusion that cannabinoids were associated with an increased risk of short-term adverse events. However, this conclusion was made based on the pooling of studies on different types of cannabinoid products across several clinical conditions. Pooled effect size estimates relating to adverse events among patients receiving THC:CBD in the treatment of chronic neuropathic or non-cancer pain were not reported separately; therefore, the pooled effect of THC:CBD on the rate of adverse events in not clear. Nevertheless, when examining the individual effect sizes of RCTs evaluating the safety of THC:CBD in patients with chronic non-cancer pain, more adverse events were associated with the use of THC:CBD than placebo. The findings from this meta-analysis warrant further study.

While the review by Jawahar et al.[17] made no specific conclusion regarding the comparative safety of THC:CBD observed across the included studies in the review, the most frequently reported adverse event in patients treated with THC:CBD was dizziness, followed by drowsiness or fatigue, vertigo, and headaches. This finding was reflected in across the other four SRs selected for inclusion in this report.

*What are the evidence-based guidelines relating to the use of delta-9-tetrahydrocannabinol/cannabidiol for adult patients with chronic non-cancer pain or neuropathic pain?*

The evidence-based guideline by Moulin et al.,[18] produced in support with the Canadian Pain Society, recommends that cannabinoids, including THC:CBD, be used as third-line agents in the management of chronic neuropathic pain, following non-response to antidepressant or anticonvulsant agents (first-line therapy), or opioid products (second-line therapy). This recommendation was made based on the SR by Lynch et al.[2], which assessed the effectiveness of smoked cannabis, THC:CBD buccal spray, and synthetic cannabinoids in comparison with placebo.

Evidence-based guidelines for the management of patients with other chronic non-cancer pain in the Canadian context were not identified in the published literature.

### Limitations

The SRs and meta-analysis included in this report appeared well designed and addressed the research questions posted. However, certain factors related to these reviews, as well as the published literature which informed the study conclusions, may limit a clear interpretation of the results and their applicability to the Canadian setting. Most notably, variation in the number, quality, and types of RCTs, as well as the different pain conditions assessed, reduces the comparability of findings across the published reviews in order to inform the true analgesic effect and safety of THC:CBD buccal spray for the pain conditions of interest in this report. Furthermore, reliance on placebo-controlled RCTs across all included reviews may be of limited utility to clinical practice given that the effectiveness of THC:CBD buccal spray is likely to be routinely used alongside other active pharmacotherapies. Although all review authors performed an assessment of the scientific quality of clinical studies selected for inclusion, the use of simplistic (4-item) quality assessment scales in two included SRs may be problematic as this tool may not permit a thorough evaluation of all relevant aspects related to a study's scientific quality; in addition, too much emphasis may be placed on items such as blinding, and this tool may be susceptive to poor consistency between different raters. This may subsequently impact the formulation of study conclusions.

The selected guideline recommendations were supported by published clinical evidence; however, there is uncertainty relating to the methodological rigour and stakeholder involvement in the guideline development process. The applicability of this guideline to clinical practice may be limited owing to the lack of high-quality evidence supporting the specified recommendations, particularly relating to the use of THC:CBD buccal spray for alleviating chronic non-cancer pain.

## CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on the identified published literature, THC:CBD buccal spray may be associated with reduced levels of perceived pain and may be well tolerated in the short term among patients with chronic neuropathic or non-cancer pain; however, the sustained benefit of these short-term clinical outcomes following longer-term therapy or discontinuation remains unclear. Given that the identified published evidence regarding the analgesic effect and safety profile of THC:CBD buccal spray for the management of chronic non-cancer pain is based wholly on moderate quality placebo-controlled trials, caution must be exercised in using this evidence to support reimbursement-based decision-making for THC:CBD in managing chronic neuropathic or non-cancer pain. This is especially important given the lack of evidence on the comparative effectiveness of THC:CBD versus other active comparators, and the high cost associated with this therapy.

The identified evidence based guideline recommends the use of THC:CBD buccal spray as third-line therapy in the management of chronic neuropathic pain. This applicability of this recommendation is limited in view of insufficient high-quality scientific evidence supporting the use of THC:CBD in chronic pain patients. No other Canadian or international evidence-based guidelines were identified relating to THC:CBD buccal spray for chronic pain management.

In brief, the available evidence comparing patient outcomes following THC:CBD treatment versus placebo appears insufficient to make well-founded conclusions about the clinical advantage and use of THC:CBD for the management of chronic neuropathic and non-cancer pain. Well-designed, prospective, randomized, active comparator-controlled trials with adequate follow-up, and adapted for the Canadian setting are needed to address this evidence gap.

**PREPARED BY:**
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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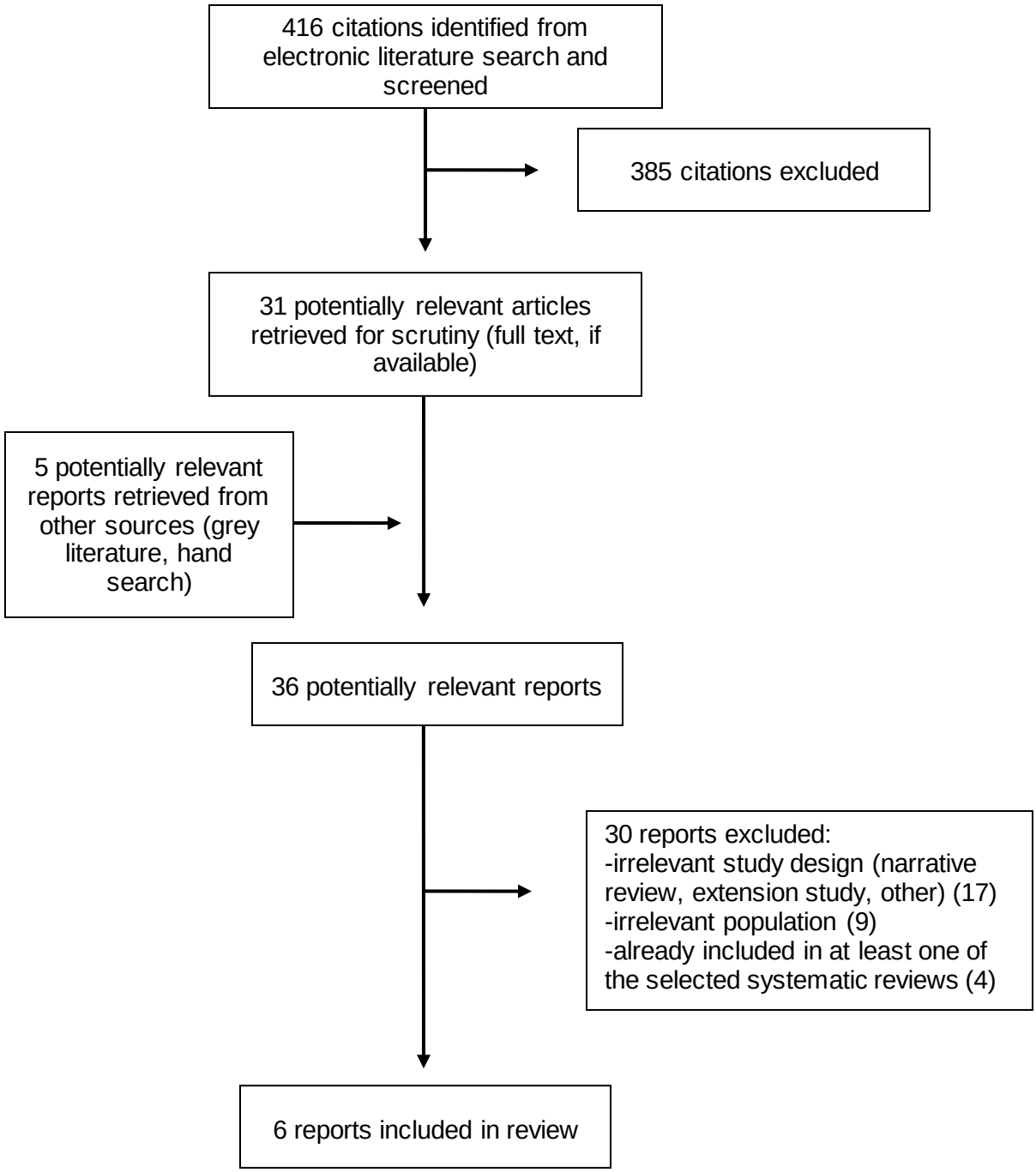
**Appendix 1: Selection of Included Studies**



## 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 and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Boychuk, 2015[14]<br>United States | 13 included studies:<br>**5 RCTs examining THC:CBD;**<br>5 RCTs examining THC (smoked and vaporized);<br>3 RCTs examining synthetic cannabinoids. | Patients with chronic non-malignant neuropathic pain. | Cannabinoids vs. placebo:<br>• Whole plant cannabinoids, delivered as smoke or vapour (e.g. smoked cannabis)<br>• Cannabinoid extracts, delivered as aerosol spray (e.g. nabiximols)<br>• Synthetic cannabinoids, ingested orally (e.g. dronabinol, nabilone, CT-3) | *Primary outcome:*<br>Reduction in pain intensity (NmRS, NPS, PDI)<br><br>*Secondary outcome(s):*<br>Adverse events<br><br>Length of follow-up within primary studies relating to THC:CBD:<br>14 weeks (1 study)<br>Not reported (4 studies) |
| Lynch, 2015[15]<br>Canada | 11 included studies:<br>**3 RCTs examining THC:CBD (1 RCT related to chemotherapy-induced pain);**<br>3 RCTs examining synthetic cannabinoids;<br>2 RCTs examining THC (smoked and vaporized);<br>1 RCT examining a FAAH inhibitor;<br>1 RCT examining an oral cannabis extract;<br>1 RCT examining gapabetin/nabilone dual therapy. | Patients with chronic non-cancer pain. | Cannabinoids vs. each other or placebo:<br>• THC (smoked or vaporized)<br>• Oral cannabis extract<br>• Oral mucosal cannabis spray (e.g. THC:CBD)<br>• FAAH inhibitor<br>• Synthetic cannabinoids (i.e. nabilone)<br>• Combination therapy (gabapentin and nabilone) | *Primary outcome:*<br>Pain relief (NmRS, BPI, NPS)<br><br>*Secondary outcome(s):*<br>Adverse events (serious adverse events, drug-related withdrawals, and frequently reported side effects);<br><br>Length of follow-up within primary studies relating to THC:CBD:<br>14 weeks (2 studies)<br>4 weeks (1 study) |

**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 and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Whiting, 2015[16]<br>United Kingdom | 79 included studies<br><br>*28 studies on chronic pain:*<br>7 RCT examining THC (smoked, capsules, vaporized, or oromucosal spray);<br>**13 RCTs examining THC:CBD (3 RCTs related to cancer pain);**<br>7 RCTs examining synthetic cannabinoids;<br>1 RCT examining gapabetin/nabilone dual therapy. | Patients with/experiencing (number of studies):<br>• Nausea and vomiting due to chemotherapy (28)<br>• Appetite stimulation in HIV/AIDS (4)<br>• **Chronic pain (28)**<br>• Spasticity due to multiple sclerosis or paraplegia (14)<br>• Anxiety disorder (1)<br>• Sleep disorder (2)<br>• Psychosis (2)<br>• Intraocular pressure in glaucoma (1)<br>• Tourette syndrome (2) | Cannabinoids vs. placebo:<br>• THC<br>• Nabiximols (THC:CBD)<br>• Synthetic cannabinoids (e.g. nabilone, dronabinol, CT-3)<br>• Combination therapy (gabapentin and nabilone) | *Primary outcome:*<br>Patient-relevant outcomes (e.g. pain relief [NmRS, VAS, NPS, BPI], discomfort, functional status)<br>Activities of daily living<br>Quality of life<br><br>*Secondary outcome(s):*<br>Adverse events<br><br>Length of follow-up within primary studies relating to THC:CBD:<br>9-15 weeks (5 studies)<br>4-5 weeks (4 studies)<br>2-3 weeks (4 studies) |
| Jawahar, 2013[17]<br>United States | 15 included studies:<br>6 studies (3 RCTs, 3 NRS) examining anticonvulsants;<br>**3 RCTs examining THC:CBD;**<br>2 RCTs examining antidepressants;<br>2 studies (1 RCT, 1 NRS) examining opioids/opioid antagonists;<br>1 RCT examining dextromethorphan/quinidine;<br>1 RCT examining dronabinol. | Patients clinically diagnosed with multiple sclerosis and experiencing non-spastic and non-trigeminal neuralgic pain. | • Antidepressants<br>• Anticonvulsants<br>• Dextromethorphan/quinidine<br>• Cannabinoids<br>• Opioids/opioid antagonists<br>• Placebo | *Primary outcome:*<br>Patient-reported pain relief (NmRS, VAS, BPI)<br><br>*Secondary outcome(s):*<br>Adverse events<br><br>Length of follow-up within primary studies relating to THC:CBD:<br>14 weeks (1 study)<br>5-6 weeks (2 studies) |

| **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 and Comparator(s)** | **Clinical Outcomes, Length of Follow-Up** |
| Lynch, 2011[2]<br>Canada | 18 included studies:<br>4 RCTs examining smoked cannabis;<br>**7 RCTs examining THC:CBD;**<br>7 RCTs examining synthetic cannabinoids. | Patients with chronic neuropathic pain or chronic non-cancer pain related to fibromyalgia, rheumatoid arthritis, and mixed chronic pain. | Cannabinoids vs. each other or placebo:<br>• Smoked cannabis<br>• Oromucosal extracts of cannabis-based medicine (e.g. THC:CBD)<br>• Synthetic cannabinoids (e.g. dronabinol, nabilone, novel THC analogue) | *Primary outcome:*<br>Pain relief (NmRS, VAS, PDI, SF-MPQ, NPS)<br><br>*Secondary outcome(s):*<br>Adverse events (serious adverse events, drug-related withdrawals, and frequently reported side effects);<br>Level of function (Barthel index).<br><br>Length of follow-up within primary studies relating to THC:CBD:<br>4-6 weeks (4 studies)<br>1-2 weeks (3 studies) |

BPI = Brief Pain Inventory; CT-3 = 1',1'-dimethylheptyl-delta-8-tetrahydrocannabinol-11-oic acid (ajulemic acid); FAAH = fatty acid amide hydrolase; NmRS = Numerical Rating Scale; NPS = Neuropathic Pain Scale; NRS = non-randomized study; PDI = Pain Disability Index; RCT = randomized controlled trial; SF-MPQ = McGill Pain Questionnaire – Short Form; THC = tetrahydrocannabinol; THC:CBD = delta-3-tetrahydrocannabinol/cannabidiol; VAS = Visual Analogue Scale; vs. = versus

**Table A2**: Characteristics of Included Guidelines

| Objectives | | | Methodology | | | |
|---|---|---|---|---|---|---|
| **Intended users/ Target population** | **Intervention and Practice Considered** | **Major Outcomes Considered** | **Evidence collection, Selection and Synthesis** | **Evidence Quality and Strength** | **Recommendations development and Evaluation** | **Guideline Validation** |
| Moulin, 2014[18] – The Canadian Pain Society | | | | | | |
| Intended users: Physicians, nurse practitioners, and other allied health care individuals involved in the management of neuropathic pain.<br><br>Target population: Patients with chronic neuropathic pain. | Pharmacological management of patients with chronic neuropathic pain. | Differential diagnosis; Therapeutic options (first-line to fourth-line agents); Stepwise pharmacological management recommendations & practice algorithm. | Systematic searches of two electronic databases for published systematic reviews, meta-analyses, and/or consensus statements; evidence summarized narratively. | Expert consensus and level of evidence (LOE) rating system proposed by the AAN. | Consensus recommendations developed based on review of evidence and strength of recommendations determined according to the AAN rating system.<br><br>Recommendations for treatment were based on the degree of evidence of analgesic efficacy, safety, and ease of use. | No evidence of guideline validation was reported. |

AAN = American Academy of Neurology

## Appendix 3: Overlap among Studies Included in Systematic Reviews and Meta-Analyses

**Table A3: Overlap Among Primary Studies Included in Systematic Reviews**

| Primary Study First Author, Publication Year | Systematic Review First Author, Publication Year | | | | |
|---|---|---|---|---|---|
| | Boychuk, 2015[14] | Lynch, 2015[15] | Whiting, 2015[16] | Jawahar, 2013[17] | Lynch, 2011[2] |
| Berman, 2004 | • | | • | | • |
| Berman, 2007 | | | • | | |
| Blake, 2006 | | | • | | • |
| GW Pharma, 2005 | | | • | | |
| GW Pharma, 2012 | | | • | | |
| Johnson, 2010[c] | | | • | | |
| Langford, 2013 | • | • | • | • | |
| Lynch, 2014[c] | | • | • | | |
| Notcutt, 2004 | | | | | • |
| Nurmikko, 2007 | • | | • | | • |
| Portenoy, 2012[c] | | | • | | |
| Rog, 2005[b] | • | | • | • | • |
| Selvarajah, 2010 | • | | • | | |
| Serpell, 2014 | | • | • | | |
| Wade, 2003 | | | | | • |
| Wade, 2004[a] | | | | • | • |

[a] = Pain reduction was not the primary outcome for the study and was not measured for the entire sample; [b] = Pain was related to spasticity in multiple sclerosis patients; [c] = Study on cancer-related pain

## Appendix 4: Critical Appraisal of Included Publications

**Table A4:** Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[12]

| Strengths | Limitations |
|---|---|
| Boychuk, 2015[14] | |
| • Duplicate article screening and data extraction was performed with a consensus procedure in place in case of disagreements.<br>• A comprehensive search of the literature (electronic databases) was performed.<br>• Methodological quality assessment of included studies was performed and documented.<br>• The scientific quality of included studies was considered in formulating conclusions of the review.<br>• Review authors disclosed potential conflicts of interest. | • Unclear whether the research questions posed or inclusion criteria used were established a priori (i.e. no evidence of review protocol or pre-defined published research objectives)<br>• Unclear whether the literature search was supplemented by a search for "grey literature".<br>• The characteristics of included studies were not provided.<br>• List of excluded studies was not provided nor referenced (only reasons for exclusion are provided).<br>• Differences in length of follow-up between included studies was not described or evaluated.<br>• Rationale for the decision to not meta-analyze the results was not described.<br>• Likelihood of publication bias was not assessed.<br>• Sources of funding of included studies were not described. |
| Lynch, 2015[15] | |
| • Duplicate article screening and data extraction was performed with a consensus procedure in place in case of disagreements.<br>• A comprehensive search of the literature (electronic databases) was performed, including a search for unpublished studies (grey literature)<br>• A list of included studies and study characteristics was provided.<br>• Methodological quality assessment of included studies was performed and documented.<br>• Review authors disclosed potential conflicts of interest. | • Unclear whether the research questions posed or inclusion criteria used were established a priori (i.e. no evidence of review protocol or pre-defined published research objectives)<br>• List of excluded studies was not provided nor referenced (only reasons for exclusion are provided).<br>• The scientific quality of included studies not mentioned in the overall conclusions of the review.<br>• Rationale for the decision to not meta-analyze the results was not described.<br>• Likelihood of publication bias was not assessed.<br>• Sources of funding of included studies were not described. |
| Whiting, 2015[16] | |
| • A priori design was used and review protocol referenced<br>• Duplicate article screening and data extraction was performed with a consensus procedure in place in case of disagreements.<br>• A comprehensive search of the literature (electronic databases) was performed, including a search for unpublished studies (grey literature)<br>• A list of included studies and study characteristics was provided. | • List of excluded studies was not provided nor referenced (only reasons for exclusion are provided).<br>• Likelihood of publication bias was not assessed.<br>• Sources of funding of included studies were not described. |

**Table A4:** Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[12]

| Strengths | Limitations |
|---|---|
| • Methodological quality assessment of included studies was performed and documented.<br>• Methods used to statistically combine results of included studies were appropriate and justified.<br>• The scientific quality of included studies was considered in formulating conclusions of the review.<br>• Review authors disclosed potential conflicts of interest. | |
| Jawahar, 2013[17] | |
| • Duplicate article screening and data extraction was performed with a consensus procedure in place in case of disagreements.<br>• A comprehensive search of the literature (electronic databases) was performed, including a search for unpublished studies (grey literature)<br>• A list of included studies and study characteristics was provided.<br>• Methodological quality assessment of included studies was performed and documented.<br>• The scientific quality of included studies was considered in formulating conclusions of the review.<br>• Review authors disclosed potential conflicts of interest and sources of funding of included studies. | • Unclear whether the research questions posed or inclusion criteria used were established a priori (i.e. no evidence of review protocol or pre-defined published research objectives)<br>• List of excluded studies was not provided nor referenced (only reasons for exclusion are provided).<br>• Rationale for the decision to not meta-analyze the results was not described.<br>• Likelihood of publication bias was not assessed. |
| Lynch, 2011[2] | |
| • A comprehensive search of the literature (electronic databases) was performed, including a search for unpublished studies (grey literature)<br>• A list of included studies and study characteristics was provided.<br>• Methodological quality assessment of included studies was performed and documented.<br>• The scientific quality of included studies was considered in formulating conclusions of the review.<br>• Decision to not meta-analyze the results was justified.<br>• Review authors disclosed potential conflicts of interest. | • Unclear whether the research questions posed or inclusion criteria used were established a priori (i.e. no evidence of review protocol or pre-defined published research objectives)<br>• Single screening of study abstracts was performed, followed by duplicate full-text article review<br>• List of excluded studies was not provided nor referenced (only reasons for exclusion are provided).<br>• Likelihood of publication bias was not assessed.<br>• Sources of funding of included studies were not described. |

| **Table A5:** Strengths and Limitations of Guidelines using AGREE II[13] | |
|---|---|
| **Strengths** | **Limitations** |
| Moulin, 2014[18] | |
| • The overall objective of the guideline is specifically described<br>• The population to whom the guideline is meant to apply is specifically described<br>• Development of the guideline appeared to include individuals from all relevant professional groups<br>• The target users of the guideline are clearly described<br>• Methods for formulating recommendations are clearly described<br>• Health benefits, side effects, and risks have been considered in formulating the recommendations<br>• There is an explicit link between the recommendations and the supporting evidence (sources were referenced)<br>• Recommendations are specific and unambiguous<br>• Different options for management of the condition are clearly presented.<br>• Key recommendations are easily identifiable<br>• Guideline provides guidance on how the recommendations can be put into practice (i.e. clinical practice algorithm described)<br>• Potential conflicts of interest are reported | • The health questions covered by the guideline are not specifically described<br>• Unclear whether the views and preferences of the patient population were sought<br>• Unclear whether systematic methods were used to search for evidence, despite mention of a systematic search<br>• Strengths and limitations of the body of evidence was not adequately described<br>• Unclear whether the guideline has been externally reviewed by experts prior to its publication<br>• Guideline does not describe facilitators and barriers to its application<br>• Guideline does not present monitoring and/or auditing criteria<br>• Unclear whether the views of the funding body have influenced the content of the guideline. |

## Appendix 5: Main Study Findings and Author's Conclusions

**Table A6:** Summary of Findings of Included Studies

| Main Study Findings | Author's Conclusions |
|---|---|
| **Systematic reviews and meta-analyses** | |
| Boychuk, 2015[14] | |
| **Reduction in pain intensity (5 RCTs):**<br>• 3 RCTs found a statistically significant reduction in mean pain intensity when comparing THC:CBD with placebo<br>  • 1 RCT reported >30% reduction in pain among patients receiving active therapy<br>• 1 RCT found no significant difference in pain (mean daily pain scores or NPS scores) between patients treated with THC:CBD and placebo<br>• 1 RCT which incorporated an enriched-enrollment randomized-withdrawal design found that there was no statistically significant difference in pain between patients treated with THC:CBD and placebo at week 14; yet, an interim analysis at week 10 showed a statistically significant difference between groups favouring THC:CBD. The authors suggested that the equivocal findings may be related to an imbalance between the mean number of daily sprays of THC:CBD and placebo.<br><br>**Adverse events (5 RCTs):**<br>• Most frequently reported adverse effects across all studies included: dizziness/vertigo, tiredness/somnolence/fatigue, dry mouth, and dysgeusia.<br>• An increased incidence of mouth ulcers, dysgeusia, and sore throat was associated with the use of THC:CBD oromucosal spray in 3 RCTs. | • "Cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments." (p.13)<br>• "[…] very few risks [were found] related to the use of cannabinoid compounds in the treatment of chronic neuropathic pain. The vast majority of adverse events listed were considered minor in nature." (p.12) |
| Lynch, 2015[15] | |
| **Pain relief (2 RCTs):**<br>• 1 RCT found a statistically significant reduction in pain (NmRS) in patients with neuropathic pain associated with allodynia who were treated with THC:CBD, as compared with patients treated with placebo.<br>• 1 RCT found a statistically significant reduction in pain (NmRS, BPI) between patients receiving THC:CBD and placebo at 10 weeks; however, at 14 weeks, pain scores did not differ between the THC:CBD and placebo groups.<br><br>**Adverse events:**<br>• Two serious AEs (<1%) were noted in 297 patients receiving THC:CBD in one RCT (disorientation, suicidal ideation); there were no treatment-related serious AEs in the other trial which examined THC:CBD in patients with chronic non-cancer pain. | • "This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain." (p.293) |

| Table A6: Summary of Findings of Included Studies | |
|---|---|
| **Main Study Findings** | **Author's Conclusions** |
| • Most common drug-related AEs across all studies (11 RCTs) included: drowsiness or fatigue, dizziness, dry mouth, nausea, and cognitive effects. | |
| Whiting, 2015[16] | |
| **Improvement in pain:**<br>• The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (OR 1.41, 95%CI = 0.99 to 2.00, 8 RCTs) (not statistically significant); one RCT assessed smoked THC and 2 of 7 trials which evaluated THC:CBD focused on cancer-related pain.<br>• The pooled treatment effect estimates in studies which assessed neuropathic pain (6 RCTs) and cancer pain (2 RCTs) favoured THC:CBD; however, these findings were not statistically significant.<br>• THC:CBD was associated with a greater average reduction in pain based on the NPS (WMD = -3.89, 95%CI = -7.32 to -0.47; 5 RCTs)<br><br>**Adverse events:**<br>• Cannabinoids were associated with a much greater risk of any AE (OR 3.03, 95%CI = 2.42 to 3.80; 29 RCTs), serious AE (OR 1.41 95%CI = 1.04 to 1.92; 34 RCTs), withdrawals due to AE (OR 2.94, 95%CI = 2.18 to 3.96; 23 RCTs)<br>• Pooled effect size estimates relating to AEs among patients receiving THC:CBD for the treatment of non-cancer or neuropathic pain were not reported separately. | • "There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. […] Cannabinoids were also associated with an increased risk of short-term AEs." (p.2648) |
| Jawahar, 2013[17] | |
| **Patient-reported pain relief (3 RCTs):**<br>• 2 RCTs which recruited patients experiencing central pain found an improvement in pain scores following treatment with THC:CBD, as compared with placebo. ($ES_1$ = -0.61; $ES_2$ = -0.13)<br>• 1 RCT which recruited patients experiencing spasticity, spasms, bladder problems, tremor, and/or non-musculoskeletal pain found no improvement in pain between patients treated with THC:CBD and placebo (ES = 0.93)<br>• The pooled ES for THC:CBD (3 RCTs, 565 participants) was 0.08 (95% CI = -0.74 to 0.89) (not statistically significant)<br><br>**Adverse events (3 RCTs):**<br>• Most frequently reported adverse event in patients receiving THC:CBD across all studies was dizziness ranging from 25% to 58%. Other adverse events included fatigue/somnolence, vertigo and headaches. | • "Our review identified anticonvulsants and off-label use of dextromethorphan/quinidine as promising treatments for chronic pain in MS. […] While some studies showed promise for nabiximols, the meta-analyses did not support its use for pain reduction." (p.1720) |

| Table A6: Summary of Findings of Included Studies | |
|---|---|
| **Main Study Findings** | **Author's Conclusions** |
| Lynch, 2011[2] | |
| **Pain relief (7 RCTs):**<br>• 5 RCTs found a statistically significant reduction in pain (VAS, NmRS or NPS) when comparing THC:CBD with placebo.<br>• 2 RCTs found no statistically significant difference in pain scores (VAS) between patients treated with THC:CBD vs. placebo; in one trial of MS patients, only 23% of patients had pain as the target symptom.<br><br>**Level of function (3 RCTs):**<br>• 1 RCT found that six of seven functional areas assessed by the PDI demonstrated significant improvement on THC:CBD as compared with placebo (MD = -5.85, *P* = 0.003), while 1 RCT noted no significant difference between patients treated with THC:CBD vs. placebo.<br>• 1 RCT noted no significant improvement in activities of daily living (Barthel index) in MS patients treated with THC:CBD, as compared with placebo.<br><br>**Adverse events (7 RCTs):**<br>• No serious AEs were noted in patients receiving THC:CBD across all trials.<br>• Most common drug-related AEs included: sedation, dizziness, dry mouth, nausea, and disturbances in concentration.<br>• Other AEs included poor coordination, ataxia, headache, paranoid thinking, agitation, dissociation, euphoria, and dysphoria. | • "Cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain." (p.742) |

AE = adverse event; CI = confidence interval; ES = effect size (Cohen's *d*); MD = mean difference; MS = multiple sclerosis; NPS = Neuropathic Pain Scale; NmRS = Numerical Rating Scale; NS = not statistically significant; OR = odds ratio; PDI = Pain Disability Index; RCT = randomized controlled trial; THC:CBD = delta-3-tetrahydrocannabinol/cannabidiol; VAS = Visual Analogue Scale; vs. versus; WMD = weighted mean difference

| Table A7: Summary of Recommendations in Included Guidelines | |
|---|---|
| **Findings and Recommendations** | **Grade/Strength of Recommendation** |
| Moulin, 2014[18] – The Canadian Pain Society | |
| • Cannabinoids are recommended as third-line agents in the management of chronic neuropathic pain. However, cannabinoids also require close monitoring, are contraindicated in patients with a history of psychosis and most of these agents are expensive.<br>• Guidelines for the specific use of THC:CBD were not provided. | • Grade of recommendation not reported.<br>• Recommendation is based, in part, on the systematic review by Lynch et al.,[2] which included seven high quality RCTs (Class I and II). |

THC:CBD = delta-3-tetrahydrocannabinol/cannabidiol

## Appendix 6: Additional References of Potential Interest

***CADTH Rapid Response reports:***

Cannabinoids for the management of neuropathic pain: review of clinical effectiveness [Internet]. Ottawa: CADTH; 2010 Jul 13. [cited 2016 May 20]. (Health technology inquiry service). Available from: https://www.cadth.ca/sites/default/files/pdf/l0197_cannabinoids_neuropathic_pain_htis-2.pdf

***Systematic review of evidence-based guidelines and consensus statements for neuropathic pain (not specific for cannabinoids or chronic pain):***

Deng Y, Luo L, Hu Y, Fang K, Liu J. Clinical practice guidelines for the management of neuropathic pain: a systematic review. BMC Anesthesiol. [Internet]. 2016 Feb 18 [cited 2016 May 20];16:12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4759966/