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

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CONTEXT AND POLICY ISSUES

Cannabis sativa is a flowering plant that has long been used as a recreational drug, and for medicinal purposes.[1,2] The main psychoactive component of cannabis is delta-9-tetrahydrocannabinol (Δ^9-THC).[2] Nabilone (Cesamet®) is an oral synthetic cannabinoid, which is licensed in Canada for treating patients with severe nausea and vomiting related to chemotherapy for cancer and who have failed to respond adequately to conventional antiemetic treatments.[2-4] Clinical trials and anecdotal reports have suggested that the use of nabilone in other medical conditions, such as appetite stimulation, anxiety, spasticity, and pain.[1,5]

Chronic pain affects approximately one in five people in developed countries and two in five in less well-resourced countries. In many circumstances, the patient's quality of life is poor due to persistent pain caused either by an ongoing illness or nerve damage caused by the disease after resolution or cure of the disease.[6]

Multiple sclerosis (MS) is a neurodegenerative disease, and is the most common cause of neurological disability in young people, with an average age of onset around 30 years and a prevalence of about 120 per 100,000 individuals in North America. The majority of patients with MS display symptoms, such as fatigue, muscle stiffness or spasticity, pain, memory problems, balance trouble, tremors, urinary disturbance, and sexual dysfunctions.[2,7]

The purpose of this review is to assess the evidence of benefits and harms related to the use of nabilone in management of chronic pain, including patients with MS. Evidence-based guidelines and recommendation for the dosing of nabilone in adults for chronic pain management will also be discussed. This report is an update of a CADTH rapid review published in 2007.

RESEARCH QUESTIONS

1.   What is the clinical effectiveness of nabilone in adults for chronic pain management?

2.   What is the clinical effectiveness of nabilone in adults with multiple sclerosis for chronic pain management?

3.   What is the clinical evidence on the safety of nabilone in adults for chronic pain management?

4.   What is the clinical evidence on the safety of nabilone in adults with multiple sclerosis for chronic pain management?

5.   What are the evidence-based guidelines and recommendations for the dosing of nabilone in adults for chronic pain management?

KEY MESSAGE

Limited evidence suggests that nabilone may be better than placebo in relieving chronic pain but its relative benefits compared to other analgesics have not been proven. Current guidelines recommend the dosage of nabilone for treating neuropathic pain be titrated gradually until target relief is obtained.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library (2011, Issue 11), 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 methodological filters were applied. The search was also limited to English language documents published between January 1, 2006 and October 13, 2011.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with chronic pain; adult patients with multiple sclerosis
Intervention	Nabilone
Comparator	Active control or placebo
Outcomes	Benefits related to chronic pain (e.g. reduction in pain and improvement in QOL); Harm (e.g. adverse events, serious adverse events, and withdrawal due to adverse events); Dosages in chronic pain.
Study Designs	Health technology assessments, systematic reviews, meta-analyses, RCTs, non-RCTs, evidence-based guidelines.

QOL=quality of life; RCTs=randomized controlled trials

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, were abstracts/conference proceedings, were included in a selected systematic review, or were published prior to 2006.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[8] RCT and non-randomized study quality were evaluated using the Downs and Black instrument.[9] The AGREE (Appraisal of Guidelines for Research and Evaluation) instrument was used to evaluate the quality of evidence-based guidelines.[10] A numeric score was not calculated for each study. Instead, the strengths and weakness of each study were summarized and described.

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search yielded 167 citations. Upon screening titles and abstracts, 142 citations were excluded, and 25 potentially relevant articles were retrieved for full-text review. Of the 25 potentially relevant reports, 14 did not meet the inclusion criteria, and thus 11 publications were included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). Four systematic reviews, two RCTs, two non-RCTs and three evidence-based guidelines met the inclusion criteria. No health technology assessments were identified.

Summary of Study Characteristics

Two of the SRs and all RCTs and non-RCTs were conducted in Canada. Three evidence-based guidelines were developed in Canada, Latin America and the UK, respectively. Details of selected SRs, RCTs and non-RCTs are presented in Appendices 2 and 3. A list of instruments used to measure pain and other outcomes is provided in Appendix 4.

Systematic reviews

A systematic review by Lynch and coworkers evaluated the efficacy of cannabinoids for the treatment of chronic non-cancer pain.[6] Cannabinoids examined in this review included smoked cannabis, extracts of cannabis based medicine that are applied to the buccal mucosa, nabilone, dronabinol and a novel THC analogue. Chronic non-cancer pain conditions included neuropathic pain (NP), fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Literature search for RCTs was performed up to October 7, 2010, without a limit on language or publication date. Eligible studies were RCTs comparing cannabinoid with a placebo or active control group where the primary outcome was pain measured by various assessment scales in subjects with chronic non-cancer pain. The methodological validity of the included studies was assessed using the modified Oxford Scale. Eighteen studies involving 776 patients met the inclusion criteria. The quality of these studies was high with a mean score of 6.1 on the 7-point modified Oxford Scale. Amongst the 18 RCTs, four compared nabilone with placebo (in 3 trials) or active control (in 1 trial). Treatment durations ranged from four to six weeks and total trial duration was up to 14 weeks. The four studies examined the effect of nabilone in various

populations, including fibromyalgia,[11] spasticity-related pain resulting from MS,[12] chronic neuropathic pain[13] and spinal pain[14]. The details of the four RCTs are presented in Table 2.

The four RCTs on nabilone identified in Lynch were included in earlier systematic reviews conducted by Zaijicek et al.,[2] Watson et al.,[15] and Martin-Sanchez et al.,[16] where different selection criteria were applied: the Zajicek review focused on MS patients, the Watson review was limited to head-to-head trials, while the Martin-Sanchez review was limited to placebo-controlled studies. Because the three reviews did not provide additional information, we summarized the evidence from the Lynch review in this report.

Randomized controlled trials

Pooyania et al. conducted a double-blinded, crossover study to assess the effect of nabilone on spasticity in patients with spinal cord injury.[17] The inclusion criteria were patients aged between 18 and 65 years, with the level of injury at C5 or below, and in whom the injury occurred more than one year ago. The patients had to have demonstrated stable neurologic level in the last six months, with moderate spasticity (Ashworth ≥3), unchanged spasticity medications (concomitant medications were not specified) for at least 30 days before enrollment, and no botulinum toxin injections for more than four months. The exclusion criteria were as follows: presence of heart disease; a history of psychotic disorders, schizophrenia or any active psychologic disorder; previously documented sensitivity to marijuana or other cannabinoid agents; severe liver dysfunction; cognitive impairment; a major illness in another body area; being pregnant or nursing mother; a history of drug dependency, having smoked cannabis less than 30 days before the onset of the study or unwilling to give up smoking during the study; or fixed tendon contractures. Twelve patients were recruited. The participants were randomized using a computerized randomization system, to receive either nabilone (0.5 mg once daily to 0.5 mg twice daily depending on the tolerance of drug/placebo-related side effects) or placebo in the first 4-week period. After a 2-week washout period, the patients were crossed over to the opposite arm. The total study duration was 10 weeks. One patient dropped out of the study from the placebo arm because of unrelated causes. The primary outcome was the Ashworth Scale for spasticity in the most involved muscle group of the body. The secondary outcome measures included the sum of the Ashworth Scale in the eight muscle groups bilaterally, and the visual analog scale (VAS) for spasticity.

Another double-blinded, crossover RCT was conducted by Ware et al.[18]. Nabilone was compared with an active control, amitriptyline in patients with fibromyalgia. Eligible patients were adult men and nonpregnant women aged 18 or older with a diagnosis of fibromyalgia. They remained on stable analgesic therapy (no details were provided) but were required to have a negative urine screen for cannabinoids at baseline. Patients were excluded if they had cancer pain, unstable cardiac disease, a history of psychotic disorder, seizure disorder, glaucoma, urinary retention, hypersensitivity to the study drugs, or were taking monoamine oxidase inhibitors. Thirty-two patients were enrolled and 29 completed the study. The study used a 2-period crossover design. Each period was of two weeks duration separated by a 2-week washout period. The primary outcome was the quality of sleep measured by the Insomnia Severity Index (ISI). The secondary outcomes included pain, which was assessed by the McGill Pain Questionnaire (MPQ).

Non-randomized controlled trials

Bestard et al. conducted a non-randomized trial of nabilone and gabapentin in the management of NP in patients with peripheral neuropathy.[19] Patients were excluded if they had an alternative diagnosis that could explain their symptoms or if an alternative source of pain made it impossible for the patients to differentiate their NP from other causes of pain. The patients without prior medications for pain 30 days before initial assessment received monotherapy of nabilone or gabapentin. Flexible dosing was used for all patients, and medication doses were titrated up gradually. The primary outcome was the degree of NP which was evaluated using a 10-cm VAS. Secondary outcomes were quality of life measured by various assessment tools, such as the Brief Pain Inventory (BPI), EuroQol 5 Domains (EQ-5D), Medical Outcomes Sleep Study Scale (MOSSS), Hospital Anxiety and Depression Scale (HADs), and Short-Form 36 Health Survey (SF-36). The patients were followed for six months. A total of 101 patients were included.

Another non-randomized prospective study was conducted by Maida et al., to evaluate the effectiveness of adjuvant nabilone therapy for pain management in patients with advanced cancer.[20] Data were collected between January 2005 and October 2006. Eligible patients had a diagnosis of cancer and survived for at least 48 hours after the initial consultation. The Edmonton Symptom Assessment System (ESAS) questionnaire was completed at baseline and at least once within 60 days of baseline. Treatment had to start on the day of initial assessment and continued for at least 48 hours. The decision to prescribe nabilone was based on the presence of severe symptom-related distress at the initial consultation. The nabilone dosage ranged from one to two mg per day. Two primary outcomes evaluated were the differences between treated and untreated patients at one month follow-up in ESAS pain scores and the differences between treated and untreated patients at one month follow-up in total morphine-sulfate-equivalent (MSE) use. When using MSE, all opioid dosages were converted to morphine sulfate equivalents according to generally accepted conversion ratios, and these calculations were summed. Statistical methods were adopted to adjust for the unbalanced baseline patient characteristics. In total, 112 patients were enrolled in the study, with 47 patients treated with nabilone and 65 untreated patients. Among the 47 patients receiving nabilone, 51% of patients were prescribed nabilone for pain relief, 26% to relieve nausea, and 23% for anorexia. The mean daily dose of nabilone was 1.79 mg. The mean duration from baseline to patient's one-month assessment was 23.8 days in the treated group and 23.2 days in the untreated group.

Guidelines

Three sets of guidelines were found. Two of these included recommendations on dosing.

Namaka and coworkers from Canada updated a treatment algorithm for NP that was developed in 2004.[21] A comprehensive search was performed to include studies published between 1980 and 2009. The authors did not describe the methods of evidence grading.

A group of Latin American experts developed guidelines for the diagnosis and management of NP.[22] Publications of management guidelines of NP were identified through multiple databases since 2003 onwards, with a special interest in those published in Latin American countries. In total, four documents from Mexico, Colombia, Ecuador and Venezuela were retrieved from the literature search. There were 17 specialists in the workgroup. They reviewed the selected reference material and presented and discussed the recommendations in a plenary session. With regards to the comments received and for the changes proposed by the plenary group, a

final report was initiated and voted on. Consensus was reached when 80% of the participants agreed. If voting for the item in consideration did not achieve the necessary 80%, new opinions and comments were incorporated until the ≥80% limit was agreed upon.

The Scottish Intercollegiate Guidelines Network (SIGN) published guidelines on the control of pain in adults with cancer in 2008.[23] Multidisciplinary guideline development groups with representation from across Scotland were involved during the process, and the groups comprised representatives from various health care areas. Literature searches were carried out from 1997 to June 2007. The guidelines will be considered for review in three years. The guideline recommendations are based on a systematic review of best available evidence. The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based (*Grade A*: at least one high quality meta-analysis, systematic review of randomized controlled trials, or randomized controlled trial with a very low risk of bias and directly applicable to the target population; or a body of evidence consisting principally of well conducted meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias directly applicable to the target population, and demonstrating overall consistency of results. *Grade B*: a body of evidence including studies rated as high quality systematic reviews of case-control or cohort studies, and high quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population, and with overall consistency of results; or extrapolated evidence from studies described in *A. Grade C*: a body of evidence including well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population and with overall consistency of results; or extrapolated evidence from studies described in *B. Grade D*: non-analytic studies, such as case reports, case series, expert opinion; or extrapolated evidence from studies described in *C*).

Summary of Critical Appraisal

Details on the critical appraisal of individual studies are presented in Appendix 5.

Systematic review

The systematic review by Lynch et al. described the research questions and selection criteria. Multiple databases were searched without limits to publication date or language. It declared conflicts of interest and funding sources. However, the identified individual RCTs had sample sizes that ranged from 13 to 96 patients and trial durations of less than 14 weeks. The number of included RCTs of nabilone was four.

Randomized controlled trials

The included RCTs described the objectives, inclusion criteria, and outcome measures of the study. Also, conflicts of interest and funding sources were reported.

The quality of the results from these RCTs may be compromised due to their sample sizes. One trial included 12 patients with pain due to spasticity and the other included 32 patients with fibromyalgia. Patients in both trials were allowed to take concomitant analgesics or medications for breakthrough pain, however no details were provided.

Non-randomized controlled trials

Both studies declared the funding sources and conflicts of interest.

Data in one of the prospective study[20] showed that patients treated with nabilone were physically weaker, with more severe pain and other symptoms. The authors adjusted the baseline differences between the groups using two statistical methods. Another limitation identified by the authors was that the investigator was not blinded to patient status when evaluating outcomes at baseline and at follow-up.

Guidelines

The guideline of the treatment for NP[21] by Namaka et al. was an update of an earlier evidence-based guideline (2004) developed by the same authors. It did not specify whether the evidence was graded and how the recommendations were generated. The evidence identified through the literature search did not find RCTs of nabilone on pain management. Their recommendations were based on existing guidelines and non-randomized controlled trials. The document was supported by manufacturer.

The Latin American guidelines[22] took into account the particular conditions of medical practice in this region, since the available North American guidelines or European guidelines do not necessarily reflect the clinical practice in Latin America. The guidelines described how the recommendations were developed.

For the SIGN guidelines, one of the coauthor received research grants from industry for writing the summary of the recommendation.[23] Details with regards to the methods and process of the development of the SIGN guidelines are not available; therefore, it was not possible to thoroughly examine the quality of these guidelines.

Summary of Findings

Details of the main study findings and authors' conclusions are presented in Appendix 6.

Clinical effectiveness of nabilone in adults for chronic pain management

Pain management

Systematic review

The systematic review by Lynch et al.[6] included four RCTs that examined the efficacy of cannabinoids in chronic non-cancer pain: one was a head-to-head trial comparing nabilone with dihydrocodeine, and three were placebo-controlled trials. The head-to-head trial indicated that for patients with chronic NP, nabilone has similar effects as dihydrocodeine on pain relief measured by pain scores in a 10 cm-VAS, even though significantly more patients treated with dihydrocodeine had a drop of more than 10 mm in the VAS. The results should be interpreted with cautions due to the high dropout rates in the study population (about one third of patients did not complete the study). When compared with placebo, nabilone significantly decreased the pain measured by VAS or 11-Point-Box-Test in patients with fibromyalgia, spasticity-related or spinal pain.

Randomized controlled trials

All participants in the Pooyania study[17] were men, with an average age of 42 years. Baseline characteristics were balanced between groups except a significantly higher baseline sum of Ashworth observed in the active treatment period than the placebo period (35.6 versus 25.1, p<0.005). This was deemed as "occurred by coincidence" by the authors. Spasticity improved significantly in the most spastic muscle group when patients were treated with nabilone, as measured by the Ashworth scale (p=0.003). It found no significant difference between the treatment and placebo periods with regards to pain relief measured by VAS (p=0.076).

In total, 32 patients were enrolled in the Ware study[18], and 29 of them completed it. The mean age in the study group was 49.5 years. Nabilone was found to have a greater effect on sleep than amitriptyline on the ISI (p<0.05); no difference was detected between treatments for pain, measured with MPQ (p>0.05).

Non-randomized controlled trials

One non-RCT compared the effectiveness of nabilone with gabapentin in patients with NP.[19] Patients in each treatment group were similar with regards to age, sex and severity of NP prior to the study initiation. Significant improvement in VAS pain scores after six months of treatment was observed for both nabilone- and gabapentin-treated patients. In the nabilone group, the VAS pain score was reduced from 45.8±11.3 (mean ± standard deviation) to 28.0±10.5; for gabapentin, the VAS pain score was reduced from 50.2±13.5 to 33.8±11.6. The authors indicated that the differences were statistically significant, but the p values were not reported. Some improvement was observed in the domain of average pain in BPI in either group as well (nabilone, decreased from 4.7±2.3 at baseline to 4.1±1.9 at 6-month; gabapentin, decreased from 4.8±2.4 at baseline to 4.2±2.0 at 6-month. P values were not provided). The results implied that the benefits (pain relief and improved QOL) of nabilone in the management of NP were comparable to gabapentin. However, there was no direct comparison between nabilone and gabapentin regarding the clinical effectiveness in pain or QOL.

Results from another non-RCT[20] indicated that cancer pain was reduced significantly in patients treated with nabilone (ESAS symptom score 3.0 versus 5.5, p<0.001) as adjunct therapy compared to no nabilone. Medication use measured by MSE was significantly reduced in treated patients (total MSE 3.7 versus 4.3, p <0.001).

Quality of Life

Systematic review

Compared with placebo, the results from the systematic review indicated that nabilone significantly improved the QOL measured by FIQ and the Mezzich & Cohen QOL-score, in patients with fibromyalgia or chronic therapy-resistant pain related to skeletal and locomotor system disorders.[6]

Non-randomized controlled trials

In one non-RCT[19] that examined the effects of nabilone in patients with NP, there were no significant improvements in EQ-5D scores, EQ health status scores, or total HADS scores at six months follow up from baseline for either nabilone or gabapentin; however, significant

improvement was observed for the domains of pain or discomfort within the EQ-5D (data not shown in the article). When assessed by SF-36, both nabilone and gabapentin therapy led to significant improvement in domains of Physical Functioning, and Bodily Pain from baseline to 6-month follow up (Physical Functioning: nabilone, increased from 35.6±25.5 to 43.7±26.4; gabapentin, increased from 35.4±25.4 to 42.6±23.4. Bodily Pain: nabilone, increased from 26.9±20.3 to 39.6±14.4; gabapentin, increased from 26.2±22.0 to 38.3±19.1. P values were not provided).

Clinical effectiveness of nabilone in adults with multiple sclerosis for chronic pain management

Randomized controlled trials

One double-blind, placebo-controlled, crossover RCT[12] was included in the Lynch review[6]. It enrolled 13 patients with spasticity-related pain resulting from MS. The data in this study showed that nabilone significantly decreased pain, while spasticity, motor function and activities of daily living did not change.

Safety of nabilone in adults for chronic pain management

Systematic reviews

The Lynch review[6] found that there were no serious adverse effects in treatment with cannabinoids. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity, and led to withdrawal from the studies in only a few cases.

Randomized controlled trials

In the Pooyania study,[17] nabilone was tolerated by all the patients. Adverse events occurred in eight out of 11 patients in the nabilone-treated period, while no patients in the placebo-treated period reported such events. No serious adverse events emerged and no dropouts due to adverse events occurred during the trial. The reported adverse events included drowsiness, dry mouth, asthenia, vertigo, mild ataxia, headache and lack of motivation.

In the Ware study,[18] a total of 187 adverse events were observed during the trial, of which 120 were mild and 64 were moderate. Two severe adverse events were reported with amitriptyline and one severe adverse event (drowsiness) occurred during nabilone therapy. It is unclear if this was treatment-related. Fifty-three adverse events were considered possibly related to amitriptyline therapy, while 91 adverse events were considered possibly related to nabilone therapy. The most common adverse events occurred in the nabilone period were dizziness nausea, dry mouth and drowsiness.

Non-Randomized controlled trials

In the Bestard study,[19] nabilone-treated patients tended to have fewer overall adverse events when compared with those treated with gabapentin (38% versus 48%). Sedation occurred in 6% of nabilone-treated patients and 15% of gabapentin-treated patients; dizziness occurred in 4% of nabilone-treated patients and 8% of gabapentin-treated patients. Patients in the nabilone group were less likely to discontinue the treatment due to drug intolerance compared with gabapentin at 6-month follow up (n=5 versus n=12). Statistical comparisons were not performed between the two treatment groups.

Clinical evidence on the safety of nabilone in adults with multiple sclerosis for chronic pain management

The Wissel study[12] which was included in the Lynch review[6] reported adverse events in five patients: one patient with moderate transient weakness of the lower limbs (nabilone phase, patient dropped out), three patients with mild drowsiness (2 in nabilone phase, 1 in placebo phase) and one patient with mild dysphagia (placebo phase). One patient was excluded from the study due to an acute relapse of MS in the nabilone phase.

Evidence-based guidelines and recommendations for the dosing of nabilone in adults for chronic pain management

The literature search identified three evidence-based guidelines.[21-23]

In the treatment algorithm developed by Namaka et al.,[21] based on the findings from the literature search, the authors indicated nabilone should be reserved as adjunctive combination therapy for breakthrough episode of NP. The dosage should be titrated gradually at weekly increments of 0.5 mg until target relief is obtained or maximal dosing of 1 mg twice daily is achieved.

The main recommendations provided by a group of Latin American experts[22] on neuropathic pain were as follows:

1) Multimodal treatment is preferred when starting therapy, in that drugs are loosely classified into four groups: A (for example, lidocaine patch), B (for example, gabapentin and fast-acting opioids), C (for example, duloxetine and slow-released opioids), and D (for example, cannabinoids); therapeutic groups show preference levels in descending order, which means that Group A is considered first, and in case of unsatisfactory response with monotherapy or combination therapy with Group A drugs, it is recommended to replace or combine with drugs from Group B, C or D.

2) For most patients, a combination of medications is recommended in cases of inadequate response from monotherapy.

3) For localized peripheral neuropathies (such as postherpetic neuralgia and diabetic neuropathy), diffuse peripheral neuropathies (such as nutritional/metabolic disorders and adverse effects related to chemotherapy), and central neuropathic pain (injury of spinal cord or brain due to trauma, inflammation, or multiple sclerosis), cannabinoids may be used when an inadequate treatment effect from drugs in Group C is observed. Recommended dose of nabilone is 0.5 mg twice daily to 1 mg twice daily.

4) No recommendation of the use of drugs in Group D for patients with mixed nonmalignant pain (such as chronic back pain caused by osteoarthritis, or herniated disc), cancer pain, or trigeminal neuralgia is provided.

The SIGN guidelines do not recommend cannabinoids for the treatment of cancer pain (Grade A recommendation).[23]

Limitations

Although most of the included individual studies were double-blind RCTs, several of these compared nabilone with placebo; therefore, the effectiveness of nabilone relative to an existing active treatment has not been adequately assessed. Quality of the individual studies varied. Methods of allocation concealment were not reported in many of the trials. The sample size of these trials (range of 13 patients to 96 patients in RCTs) does not allow us to make solid conclusions from the study findings. The duration of the trials ranged from four weeks to 14 weeks. Evidence of longer-term benefits and harms of nabilone in chronic pain management is lacking.

The etiologies of chronic pain evaluated in this review were different (for example, neuropathic pain, cancer pain, spasticity, fibromyalgia etc.). It, therefore, is a challenge to synthesize data from the varied populations. Moreover, the evidence of effectiveness of nabilone on MS patients is sparse. The only available data were identified from one RCT that recruited 13 patients.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In total, four SRs, two RCTs, two non-RCTs and three evidence-based guidelines are included in this review. The conditions examined in these studies include non-cancer pain, such as NP, fibromyalgia, spasticity-related pain resulting from MS and spinal pain, and cancer pain.

Evidence from these placebo-controlled trials indicated that nabilone statistically significantly reduces severity of pain in patients with chronic non-cancer pain. Limited evidence from head-to-head trials suggests that nabilone was not better than an existing analgesic agent (dihydrocodeine and amitriptyline) in pain management. An RCT of 13 MS patients found that nabilone was more efficient in spasticity-related pain. A solid conclusion regarding the clinical effectiveness of nabilone on chronic pain management cannot be made based on the available evidence. Overall, nabilone was well-tolerated among the study populations, where the most common adverse events included dizziness, nausea and dry mouth.

The current evidence-based guidelines recommend the dosage of nabilone for treating neuropathic pain should be titrated gradually at weekly increments of 0.5 mg until target relief is obtained or maximal dosing of 1 mg twice daily is reached.

The majority of the studies were conducted in Canada, which may be more helpful in guiding the use of nabilone in chronic pain management in the Canadian population. Additional well-designed, large-scale randomized trials with longer-term follow-up are required to evaluate the clinical effectiveness and safety of nabilone in patients with chronic pain.

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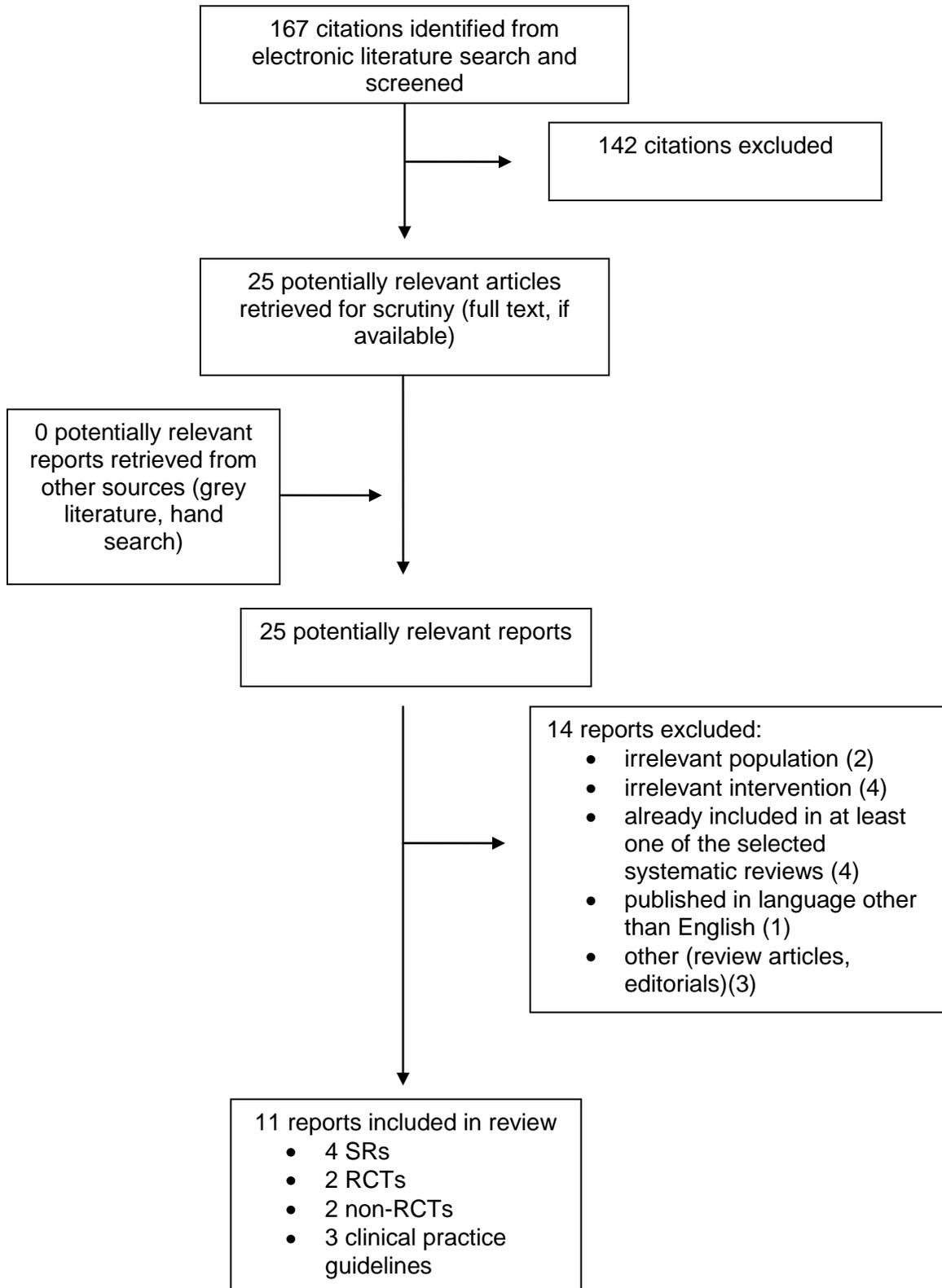Canadian Agency for Drugs and Technologies in Health
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APPENDIX 1: Selection of Included Studies

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        ┌─────────────────────────────┐
        │ 167 citations identified from│
        │ electronic literature search │
        │         and screened         │
        └─────────────────────────────┘
                    │        ┌──────────────────────────┐
                    │───────▶│  142 citations excluded   │
                    │        └──────────────────────────┘
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        ┌─────────────────────────────┐
        │ 25 potentially relevant      │
        │ articles retrieved for       │
        │ scrutiny (full text, if      │
        │         available)           │
        └─────────────────────────────┘
┌──────────────────────┐     │
│ 0 potentially relevant│     │
│ reports retrieved from│────▶│
│ other sources (grey   │     │
│ literature, hand      │     │
│       search)         │     │
└──────────────────────┘     ▼
        ┌─────────────────────────────┐
        │ 25 potentially relevant      │
        │          reports             │
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┌──────────────────────────────────────┐
│ 14 reports excluded: │
│   • irrelevant population (2)   │
│   • irrelevant intervention (4)   │
│   • already included in at least   │
│   one of the selected   │
│   systematic reviews (4)   │
│   • published in language other   │
│   than English (1)   │
│   • other (review articles,   │
│   editorials)(3)   │
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┌──────────────────────────────────────┐
│ 11 reports included in review   │
│   • 4 SRs   │
│   • 2 RCTs   │
│   • 2 non-RCTs   │
│   • 3 clinical practice   │
│   guidelines   │
└──────────────────────────────────────┘

Appendix 2. Summary of Study Characteristics for Systematic Review

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Lynch, 2011, Canada[6]	SR Included 18 RCTs of cannabinoids; nabilone was examined in 4 DB crossover or parallel RCTs (described below)	Chronic non-cancer pain: NP, fibromyalgia, spasticity related pain, and pain related to skeletal and locomotor system diseases	Nabilone 0.25-2mg/day	Dihydrocodeine* 240mg/day Or placebo	Pain score in VAS or other scales QOL
RCTs included in the Lynch review					
Frank et al., 2008[13]	DB, crossover, active-controlled, 96 patients enrolled Trial duration: 14 weeks, including two 6-week treatment periods and one 2-week washout period	Chronic NP	Nabilone 2mg/day + concomitant analgesics	Dihydrocodeine‡ 240mg/day + concomitant analgesics	Pain score in VAS QOL measured with SF-36
Skrabek et al., 2008[11]	DB, placebo-controlled, parallel, 40 patients randomized Trial duration: 4 week treatment and 4 week follow-up	Fibromyalgia	Nabilone 1-2mg/day + other oral medications for fibromyalgia	Placebo + other oral medications for fibromyalgia	Pain score on VAS QOL measured with FIQ
Wissel et	DB, crossover,	Spasticity-	Nabilone	Placebo	Pain score in

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
al., 2006[12]	placebo-controlled, 13 patients randomized Trial duration: 9 weeks, including two 4-week treatment periods and 1-week washout period	related pain resulting from MS	1mg/day + concomitant analgesic therapy	+ concomitant analgesic therapy	11-Point-Box-Test
Pinsger et al., 2006[14]	DB, crossover, placebo-controlled, 30 patients randomized Trial duration: 14 weeks, including two 4-week treatment periods and washout period	Chronic therapy-resistant pain related to skeletal and locomotor system disorder	Nabilone 0.25-1mg/day + standard therapy	Placebo + standard therapy	Spinal pain intensity in VAS QOL measured with Mezzich & Cohen QOL-score

DB=double-blind; FIQ=Fibromyalgia Impact Questionnaire; MS=multiple sclerosis; NP=neuropathic pain; QOL=quality of life; RCT=randomized controlled trial; SF-36=Short Form-36 Health Survey; SR=systematic review; VAS=visual analogue scale
* a codeine derivative not available in Canada

Appendix 3. Summary of Study Characteristics for RCTs and non-RCTs

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Pooyania, 2010, Canada[17]	DB, placebo-controlled crossover RCT 12 patients enrolled, study duration 10 weeks	Spasticity related to spinal cord injury	Nabilone 0.5-1mg/day + concomitant medications for spasticity	Placebo + concomitant medications for spasticity	Spasticity measured by Ashworth scale Pain score in VAS
Ware, 2010, Canada[18]	DB, active-controlled crossover RCT 32 patients enrolled, study duration 10 weeks	Fibromyalgia	Nabilone 0.5-1mg/day + concomitant analgesic therapy	Amitriptyline 10-20mg/day + concomitant analgesic therapy	Sleep quality measured by ISI Pain measured with MPQ
Bestard, 2011, Canada[19]	Non-RCT, prospective study 101 patients enrolled	NP	Nabilone 3mg/day 49 patients	Gabapentin 2.3mg/day (mean) 52 patients	VAS pain scores QOL measured by various tools
Maida, 2008, Canada[20]	Non-RCT, prospective study 112 patients enrolled	Cancer pain	Nabilone 1-2mg/day + concomitant palliative care 47 patients	No nabilone + concomitant palliative care 65 patients	ESAS pain score Medication use measured by MSE

DB=double-blind; ESAS=The Edmonton Symptom Assessment System; ISI=Insomnia Severity Index; MPQ=McGill Pain Questionnaire; MSE=morphine-sulfate-equivalent; NP=neuropathic pain; QOL=quality of life; RCT=randomized controlled trial; VAS=visual analogue scale

APPENDIX 4: Instruments Used in the Studies Reviewed in this Report

Ashworth scale
This is a common clinical approach to the routine measurement of levels of spasticity, higher score indicates more severe spasticity.[17]

ESAS
The Edmonton Symptom Assessment System is a 10-item, patient- or caregiver-rated, validated tool to assess the most prevalent symptoms in palliative care patients. The severity of the 10 items, including pain, was rated on a 10-point scale, with 0=absence of the symptom and 10=the worst possible severity.[20]

FIQ
Fibromyalgia Impact Questionnaire is a validated, self-administered test, scored out of 100, that evaluates physical function, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being in patients with fibromyalgia. Higher score indicates greater impact of fibromyalgia on the patient's quality of life.[11]

ISI
Insomnia Severity Index is a reliable and valid instrument used to quantify perceived insomnia severity and is used as an outcome measure in insomnia treatment research. Higher score indicated poorer sleep quality.[18]

MPQ
McGill Pain Questionnaire is a validated instrument frequently used in clinical trials of analgesic medications.[18]

VAS
Visual analog scale is an unmarked 10 cm line between anchors of "no pain" on the left (0) and "worst possible pain" on the right (10). It was demonstrated as valid and reliable in rating pain intensity.[19]

11-Point-Box-Test
This is a measure of spasticity-related pain, in which patients rated their pain from 0 to 10 (11-point scale), with 0 representing no pain and 10 representing the other extreme of pain intensity.[12]

APPENDIX 5: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Systematic review		
Lynch, 2011, Canada[6]	• Research questions and selection criteria clearly provided • Comprehensive literature search based on pre-defined criteria, no limits on date or language • Methods were used to minimize reviewer errors and bias in the selection of studies, assessment of validity, and data extraction • List of included studies provided • Conflicts of interest stated	• Included RCTs were small, with short trial durations • List of excluded studies not provided • List of study characteristics lacked detail
Randomized controlled trials		
Pooyania, 2010, Canada[17]	• Objectives, inclusion criteria, and outcome measures clearly described • Patients and clinicians were blinded to the treatment • Adequate method of randomization • Results were appropriately reported • Compliance with the intervention was reliable	• No power calculation • Small sample size (n=12) makes it difficult to reach firm conclusion • Number of loss to follow-up unable to determine • Study mostly focused on spasticity; pain was a secondary outcome
Ware, 2010, Canada[18]	• Objectives, inclusion criteria, and outcome measures clearly described • Allocation concealment unclear • Adequate method of randomization Patients, nurses and clinicians were blinded to the treatment • Results were appropriately reported • Loss to follow-up was reported • Sample size estimation provided	• Small sample size (n=32) makes it difficult to reach firm conclusion • Pain was not primary outcome
Non-Randomized controlled trials		

First Author, Publication Year	Strengths	Limitations
Bestard, 2011, Canada[19]	• Objectives, inclusion criteria, and outcome measures clearly described • Statistical methods to adjust for baseline differences were adopted • Results were appropriately reported • Potential confounders identified	• Non-randomized study design led to unbalanced baseline characteristics, even if statistical methods were used to adjust the unbalance • No sample size calculation
Maida, 2008, Canada[20]	• Objectives, inclusion criteria, and outcome measures clearly described • Results were appropriately reported	• Patients had cancer and used nabilone as adjuvant treatment (only 50% of nabilone patients were treated for pain; the remainder were treated for nausea or anorexia) • No sample size calculation • Potential confounders not identified

APPENDIX 6: Summary of Findings for Chronic Pain Management from SRs and RCTs

First Author, Publication Year	Main Study Findings	Conclusions
Systematic review		

Lynch, 2011[6] (results from 4 primary studies[11-14])	4 RCTs compared nabilone with placebo or active control. Number of patients ranged from 13 to 96. Trial durations were less than 14 weeks, and treatment duration of the study drug ranged from 4 to 6 weeks.
	
	Compared to placebo:
	-Significant decrease in pain measured by VAS or 11-Point-Box-Test in patients with fibromyalgia, spasticity-related or spinal pain.
	-QOL measured by FIQ:
	    Decreased from baseline for nabilone: -12.7, p<0.02
	-QOL measure by Mezzich & Cohen QOL-score:
	    Increased from baseline:
	    Nabilone:
	    5.0(0.8;10.8)(median[interquartile])
	    Placebo: 2.0(-2.3,8.0)
	
	Compared to dihydrocodeine[13] in patients with NP:
	- Both agents resulted in approximately a 10mm reduction in VAS:
	    Baseline 69.6mm (range 29.4-95.2);
	    Study end:
	    Nabilone 59.9±24.4 (mean±SD)mm,
	    Dihydrocodeine 58.6±24.1 mm.
	-Number of patients with ≥10mm drop in VAS:
	    Nabilone: 3/64*
	    Dihydrocodeine: 12/64*, significant difference
	-QOL measured by SF-36:
	    SF-36 data better with dihydrocodeine.
		Nabilone may be better than placebo in relieving chronic pain; its relative benefits compared to other analgesics (e.g. dihydrocodeine) were not proven.

Randomized controlled trials		
Pooyania, 2010[17]	Ashworth in most involved muscle group: Mean at baseline: 7.63 Mean after placebo period: 7.45 Mean after treatment period: 6.54 Mean difference±SD between treatment and placebo: 0.91±0.85, p=0.003	Nabilone reduced spasticity in people with spinal cord injury. No significant difference in pain relief with compared with

First Author, Publication Year	Main Study Findings	Conclusions
		placebo.
	VAS: Mean at baseline: 46.18 Mean after placebo period: 53.18 Mean after treatment period: 44.09 Mean difference±SD between treatment and placebo: 9.09±16.97, p=0.076	
Ware, 2010[18]	ISI: Difference between groups: -3.25 (95%CI -5.26, -1.24) MPQ: Difference between groups: -0.1 (95%CI -0.3, 0.2)	Nabilone was effective in improving sleep in patients with fibromyalgia and well tolerated. Nabilone had no effects on pain relief.

CI=confidence interval; FIQ=Fibromyalgia Impact Questionnaire; ISI=Insomnia Severity Index; MPQ=McGill Pain Questionnaire; NP=neuropathic pain; QOL=quality of life; RCT=randomized controlled trial; SD=standard deviation; SF-36=Short-Form 36 Health Survey; SR=systematic review; VAS=visual analog scale
*Per protocol dataset