Cannabinoids for the Treatment of Chronic Pain: A Critical Review of Randomized Controlled Trials

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Abstract

Persistent or Chronic pain (CP) continues to be one of the most challenging health problems in Canada. CP is estimated to affect around 29% of the Canadian population and accounts for up to 78% of clinical visits [2-4]. The impact of CP is enormous, as it leads to a severe decline in the quality of life as well as a startling rise in the incidence of disability. Many approaches including pharmacological, physical and psychological have been proposed for CP treatment. Yet these options have always been associated with either significant side effects or insignificant efficacy on the long run. Notably, many patients, suffering from CP conditions, are now using cannabinoids, even without a prescription. As a result, an exceeding number of patients are making extraordinary claims about how using marijuana have alleviated their pain. But the medical field thus far has not reached the same level of certainty. This situation has framed compelling reasons to explore the true effectiveness of cannabinoids for CP. The purpose of this paper is to critically review methodological quality and outcome measures used by RCTs investigating the effectiveness of cannabinoids to determine the real effect in such trials.

Keywords: Cannabinoids; Chronic pain; Quality of life

Introduction

Persistent or Chronic pain (CP) continues to be one of the most challenging health problems in Canada [1]. CP is estimated to affect around 29% of the Canadian population and accounts for up to 78% of clinical visits [2-4]. The impact of CP is enormous, as it leads to a severe decline in the quality of life as well as a startling rise in the incidence of disability. CP is not only associated with serious health consequences, but it also poses serious societal implications [5,6]. In 2010, the Chronic Pain Association of Canada reported that “…the annual cost of chronic pain, including medical expenses, lost income, and lost productivity is estimated to exceed $10 billion” [6]. Many approaches including pharmacological, physical and psychological have been proposed for CP treatment. Yet these options have always been associated with either significant side effects or insignificant efficacy on the long run [7].

Cannabinoids have been used in one form or another for pain treatment for a long time [8]. Notably, many patients, suffering from CP conditions, are now using cannabinoids, even without a prescription. As a result, an exceeding number of patients are making extraordinary claims about how using marijuana have alleviated their pain and turned their lives around for the better [9]. But the medical field thus far has not reached the same level of certainty. In many cases, health care providers are reluctant to support the claimed outstanding benefits for cannabinoids.

This situation has framed compelling reasons to explore the true effectiveness of cannabinoids for CP. Moreover, the increasing number of patients using cannabinoids highlights the urgent need to provide solid evidence. This evidence is needed either to support or prevent such treatment before we witness another epidemic that we cannot control, similar to what we now face with opioids [10].

So what does the scientific literature say?

Since randomized controlled trials (RCTs) are considered as the only reliable method for establishing evidence for effective therapy [11], the purpose of this paper is to critically review methodological quality and outcome measures used by RCTs investigating the effectiveness of cannabinoids to determine the real effect in such trials. First, I will review published RCTs. Second, I will appraise the methods utilized. Then, with this background, I will discuss the reliability of their conclusions concerning the efficacy that was tested and its implications for theory, research and practice.

Methods

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Inclusion criteria

Types of studies: Only RCTs comparing a cannabinoid with a placebo or active control group were included. An RCT is defined as “a study design that randomly assigns participants into an experimental group or a control group. As the study is conducted, the only expected difference between the control and experimental groups in an RCT is the outcome variable being studied”.

Types of patients

Studies dealing with adults (18 and more years of age) who have CP defined as “Persistent pain, lasting for more than 3 months beyond time needed for tissue healing” [12]. CP is usually presented as an assorted set of conditions that includes chronic back pain, chronic headaches, temporomandibular disorder, fibromyalgia, myofascial pain, neuropathic pain, HIV neuropathy, rheumatoid arthritis, and osteoarthritis.

Types of interventions

Cannabinoids (such as plant-based cannabinoids (Nabiximol) or synthetic cannabinoids (e.g., cannabidiol, dronabinol, nabilone) at

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any dose, by any route, administered for the relief of CP, compared to placebo or any active comparators were included.

**Types of outcome measures**

Outcomes were selected based on the list suggested by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [13]. The review groups have developed a set of six domains that should be assessed in RCTs investigating the efficacy of any treatment compared to another or to placebo (Table 1).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>• 11-point (0–10) numerical rating scale of pain intensity</td>
</tr>
<tr>
<td></td>
<td>• Usage of rescue analgesics</td>
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<tr>
<td></td>
<td>• Categorical rating of pain intensity (none, mild, moderate, severe)</td>
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<tr>
<td>Physical functioning</td>
<td>• Multidimensional Pain Inventory Interference Scale</td>
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<td></td>
<td>• Brief Pain Inventory interference items</td>
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<tr>
<td>Emotional functioning</td>
<td>• Beck Depression Inventory Profile of Mood States</td>
</tr>
<tr>
<td>Global improvement and satisfaction with treatment</td>
<td>• Patient Global Impression of Change</td>
</tr>
<tr>
<td>Symptoms and adverse events</td>
<td>• Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts</td>
</tr>
<tr>
<td>Participant disposition</td>
<td>• Detailed information regarding participant recruitment and progress through the trial, including all information specified in the CONSORT guidelines.</td>
</tr>
</tbody>
</table>

Table 1: Recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness.

**Search strategy**

An online search was performed in MEDLINE (via Ovid) and The Cochrane Library (via Wiley) database for studies published in the English language until 15th March 2017. Search terms used were included in full (Appendix A). The reference lists of all identified papers were searched for additional potentially relevant publications.

All articles were screened using the inclusion criteria. If the criteria were met, the full text was then reviewed for eligibility. Only full publications were selected, while abstracts, nonrandomized, studies of experimental pain, case reports, and clinical observations were all excluded.

**Methodological quality assessment**

Selected RCTs were assessed for scientific quality using a validated quality instrument; the Consolidated Standards of Reporting Trials (CONSORT) 2010. The consort statement comprises a 25-item checklist. The consort tool is developed to enable readers to understand a trial’s design, conduct, analysis and interpretation, and to assess the validity of its results.

**Assessment of risk of bias**

To assess the risk of bias, the Jadad scale was used [14]. This instrument is used to measure the likelihood of bias especially in pain research and to evaluate the impact of blinding on the findings. The instrument is simple, short, reliable, and valid. It contains three items (Randomization, Double Blinding, and Withdrawals & Dropouts). Items are rated based on the quality of the description of the methods utilized in randomization and/or on the quality of the description of the method employed in blinding.

**Results**

Five-hundred and twenty-six potentially eligible articles were
found from the search strategies and 11 other potential articles through review of the references. Fifty relevant studies were subjected to full-text review (Figure 1). Altogether, this review identified 21 RCTs.

### Assessment of trials quality according to CONSORT

#### Study characteristics

All selected trials were identified as RCTs in the title, with a structured abstract for methods, results and conclusions included. All trials provided a scientific background and explained briefly the reason behind the trials. They all determined the outcomes whether primary or secondary and proposed that cannabinoids might show more pain relief compared to placebo or the compared drug. All 21 trials were conducted from 2003 to 2014, investigating cannabinoids in different forms with a mean duration of treatment of 3.4 weeks (Table 2).

13 of the 21 trials were in neuropathic pain [15-24], another in chronic motor neuron syndrome and one in chronic headaches [25,26].

<table>
<thead>
<tr>
<th>#</th>
<th>Study</th>
<th>Design</th>
<th>Type of Chronic Pain</th>
<th>Study Sample Exp. / Control</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome</th>
<th>Results</th>
<th>Side effects &amp; Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blake et al.[2]</td>
<td>Parallel</td>
<td>Rheumatoid arthritis</td>
<td>29</td>
<td>Oromucosal spray 2.7mg THC &amp; 2.5CBD vs Placebo spray</td>
<td>5 weeks</td>
<td>Pain Sleep</td>
<td>Significant decrease in pain intensity and improved sleep</td>
<td>Not mentioned</td>
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<td>2</td>
<td>Skrabek et al.[5]</td>
<td>Parallel</td>
<td>Fibromyalgia</td>
<td>20</td>
<td>Nabulone 1mg/d orally vs Placebo</td>
<td>4 weeks</td>
<td>Pain (VAS) Anxiety HRQL</td>
<td>Significant reduction in pain, anxiety and in quality of life</td>
<td>7 withdrawals due to dry mouth, &amp; drowsiness</td>
</tr>
<tr>
<td>3</td>
<td>Ware et al.[6]</td>
<td>Crossover</td>
<td>Fibromyalgia</td>
<td>21</td>
<td>Nabulone 1mg/d orally Vs Amitriptyline 10-20 mg</td>
<td>2 weeks</td>
<td>Pain (NRS, McGill questionnaire) Sleep HRQL</td>
<td>No difference</td>
<td>3 withdrawals Due to side effects: sedation &amp; dry mouth and loss of effectiveness</td>
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<tr>
<td>4</td>
<td>Notcutt et al.[39]</td>
<td>Crossover</td>
<td>Chronic pain</td>
<td>34</td>
<td>Sublingual THC vs cannabisol vs both combo vs placebo</td>
<td>12 weeks</td>
<td>Pain Sleep BDI</td>
<td>THC &amp; both combo were superior to placebo</td>
<td>5 withdrawals Nausea vomiting depression</td>
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<tr>
<td>5</td>
<td>Pinsger et al.[27]</td>
<td>Crossover</td>
<td>Chronic pain</td>
<td>30</td>
<td>Nabulone 0.25-1mg/d orally vs Placebo</td>
<td>16 weeks</td>
<td>Pain (VAS) HRQL</td>
<td>Significant reduction in pain and improvement in quality of life</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>6</td>
<td>Narang et al.[38]</td>
<td>Crossover</td>
<td>Chronic pain</td>
<td>29</td>
<td>Dronabinol 20 mg orally vs placebo</td>
<td>4 weeks</td>
<td>Pain (VAS, BPI) HADS Sleep</td>
<td>Significant pain relief</td>
<td>3 dropped out Dry mouth, dizziness</td>
</tr>
<tr>
<td>7</td>
<td>Pini et al.[4]</td>
<td>Crossover</td>
<td>Chronic Headaches</td>
<td>26</td>
<td>Nabulone 0.5mg/day vs Ibuprofen 400 mg/day</td>
<td>2 weeks</td>
<td>Pain (VAS)</td>
<td>Nabulone was superior to ibuprofen in reducing pain intensity</td>
<td>4 dropped out for lack of efficacy</td>
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<tr>
<td>8</td>
<td>Wissel et al.[8]</td>
<td>Crossover</td>
<td>Chronic upper motor neuron Syndrome</td>
<td>13</td>
<td>Nabulone 1mg orally vs Placebo</td>
<td>1 week</td>
<td>Pain (11-piont text box)</td>
<td>Significant decrease in pain ratings</td>
<td>2 withdrawals weakness in LL Dizziness, Vertigo, drowsiness</td>
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<tr>
<td>9</td>
<td>Ellis et al.[54]</td>
<td>Crossover</td>
<td>HIV-Neuropathy</td>
<td>34</td>
<td>Cannabis (1%-8% THC) smoked vs Placebo</td>
<td>5 days</td>
<td>Pain (Vas &amp; McGill questionnaire)</td>
<td>Significant reduction in pain</td>
<td>6 withdrawals Concentration difficulties, fatigue, sleepiness or sedation, Increased duration of sleep, reduced salivation, and thirst.</td>
</tr>
<tr>
<td>10</td>
<td>Abrams et al.[15]</td>
<td>Parallel</td>
<td>HIV-Neuropathy</td>
<td>27</td>
<td>Cannabis (3.56% THC) smoked vs Placebo</td>
<td>5 days</td>
<td>Pain (VAS)</td>
<td>Significant decrease in pain</td>
<td>No withdrawals No side effects</td>
</tr>
<tr>
<td>11</td>
<td>Wilsey et al.[22]</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>38</td>
<td>Cannabis (7% THC) smoked vs Placebo</td>
<td>21 days</td>
<td>Pain (VAS)</td>
<td>Significant reduction in pain</td>
<td>6 withdrawals Some acute cognitive effects, particularly with memory, at higher doses</td>
</tr>
</tbody>
</table>

### Methods

#### Trial design

All 21 studies were double-blinded, 15 used a crossover design [27-30]. In parallel RCTs, the baseline for patients assigned to one group may have significant differences from those allocated to the other group. Hence, it is very important to routinely collect baseline data before treatment begins. Nevertheless, Toth and his colleagues did not report any baseline measurements in their trial.

#### Participants

The 21 trials involved a total of 1614 participants that met the inclusion criteria. The inclusion criteria for recruiting patients for all trials were mainly patients diagnosed with the pain condition under investigation, age 18 years and older.

A significant part of any study design is the standardized definition and diagnosis criteria of the entity under investigation, one of the
and on various doses or other non-pharmacological approaches (e.g., getting documented in any health records or used concomitant drugs counter medications without ever seeking medical assistance or the drug under investigation [32]. The duration of CP condition was considered neither as selective criteria of their condition, while distinctions should have been made. Moreover, trials collectively analysed the results for all patients together regardless recruited patients with different types of CP condition. Then, these further investigations to confirm the diagnosis [31]. Three trials were only satisfied by patients' statements on their diagnosis without contrast, other trials used telephone or surveys to recruit patients and the guidelines criteria conventionally used for patients' diagnosis. In this review, only 4 trials stated the exact definition for the pain condition they investigated together with the guidelines criteria conventionally used for patients' diagnosis. In contrast, other trials used telephone or surveys to recruit patients and were only satisfied by patients' statements on their diagnosis without further investigations to confirm the diagnosis [31]. Three trials recruited patients with different types of CP condition. Then, these trials collectively analysed the results for all patients together regardless of their condition, while distinctions should have been made. Moreover, the duration of CP condition was considered neither as selective criteria nor as a confounding factor that might have affected the effectiveness of the drug under investigation [32].

For many CP conditions, many patients used either over the counter medications without ever seeking medical assistance or getting documented in any health records or used concomitant drugs and on various doses or other non-pharmacological approaches (e.g., physical therapy). However, none of the RCTs included this criterion as a selective one. Although such criterion provided the opportunity to evaluate potential pharmacodynamics interactions, nevertheless, it was not considered as a confounding factor in the 21 trials.

Patients who had past history of smoking cannabis were not excluded from the trials, which had added to the heterogeneity to the trials. Although these subjects represent typical clinical CP patients, a physical therapy). However, none of the RCTs included this criterion as a selective one. Although such criterion provided the opportunity to evaluate potential pharmacodynamics interactions, nevertheless, it was not considered as a confounding factor in the 21 trials.

The sample size used in all selected 21 trials ranged from 13 to 128 patients who had past history of smoking cannabis were not excluded from the trials, which had added to the heterogeneity to the trials. Although these subjects represent typical clinical CP patients, a more homogeneous sample may have had a different outcome [33].

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The sample size used in all selected 21 trials ranged from 13 to 128 with relatively small sample sizes; therefore, all findings regarding the efficacy of cannabinoids were questionable.

Intervention

CP is a chronic disease, expected to persist for lifetime and treatment is expected to be utilized for long periods of time. To assess the efficacy

<table>
<thead>
<tr>
<th>Ref</th>
<th>Design</th>
<th>Condition</th>
<th>No.</th>
<th>Dose</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcome</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>38</td>
<td>44</td>
<td>Cannabis (7.7%) smoked vs placebo</td>
<td>14 days</td>
<td>Pain (VAS) PGIC</td>
<td>No withdrawals</td>
</tr>
<tr>
<td>13</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>23</td>
<td>23</td>
<td>THC (6%) 25mg/d vs placebo</td>
<td>2 weeks</td>
<td>Pain (VAS, NRS McGill questionnaire) Sleep (Leeds Sleep evaluation questionnaire) HRQL</td>
<td>Improved sleep &amp; significantly lower pain intensity</td>
</tr>
<tr>
<td>14</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>63</td>
<td>62</td>
<td>Nabixmols: THC (30mg)/ Cannabidiol (27.5mg) oromucosal spray vs Placebo</td>
<td>5 weeks</td>
<td>Pain (NRS) Sleep PGIC</td>
<td>Significant decrease in pain &amp; improved sleep</td>
</tr>
<tr>
<td>15</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>48</td>
<td>48</td>
<td>Nabixmols: THC (12.6mg)/ Cannabidiol (120mg) oromucosal spray vs Placebo</td>
<td>2 weeks</td>
<td>Pain Sleep SF-MPQ PDI</td>
<td>Significant decrease in pain and sleep improvement</td>
</tr>
<tr>
<td>16</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>21</td>
<td>21</td>
<td>CT-3 (4 X 10 mg) vs placebo</td>
<td>7 days</td>
<td>Pain (VAS)</td>
<td>Reduction in pain scores</td>
</tr>
<tr>
<td>17</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>20</td>
<td>20</td>
<td>THC (2.5 mg) vs CBD vs Nabixmols (120 mg) vs placebo</td>
<td>10 weeks</td>
<td>Pain (VAS) THC &amp; CBD were superior to placebo</td>
<td>3 dropped out due to hypotension</td>
</tr>
<tr>
<td>18</td>
<td>Parallel</td>
<td>Neuropathic pain</td>
<td>66</td>
<td>66</td>
<td>Nabixmols vs placebo</td>
<td>5 weeks</td>
<td>Pain (NRS) Sleep HADS PGIC</td>
<td>Significant decrease in pain intensity and improved sleep</td>
</tr>
<tr>
<td>19</td>
<td>Crossover</td>
<td>Neuropathic pain</td>
<td>48</td>
<td>48</td>
<td>Dihydrocodeine 240 mg vs naboline 2mg orally</td>
<td>12 weeks</td>
<td>Pain (VAS) Depression (Hamilton) SF-36</td>
<td>Dihydrocodeine provided better pain relief</td>
</tr>
<tr>
<td>20</td>
<td>Parallel</td>
<td>Diabetic neuropathy</td>
<td>25</td>
<td>26</td>
<td>Nabilone vs placebo</td>
<td>5 weeks</td>
<td>Pain (NRS) Function (BPI) QOL (EQ-5D)</td>
<td>Nabilone was statistically more effective in reducing pain intensity, improvement in sleep and anxiety</td>
</tr>
<tr>
<td>21</td>
<td>Parallel</td>
<td>Peripheral neuropathy</td>
<td>128</td>
<td>118</td>
<td>Oromucosal cannabis vs placebo</td>
<td>15 weeks</td>
<td>Pain (NRS) Function (BPI) QOL (EQ-5D) Satisfaction (PTSS) Mood (HADS) Sleep (MOSS)</td>
<td>Statistically significant reduction in pain &amp; improvements in pain and GIC</td>
</tr>
</tbody>
</table>

Table 2: Summary of efficacy in single studies.

Challenges faced in pain research. In this review, only 4 trials stated the exact definition for the pain condition they investigated together with the guidelines criteria conventionally used for patients' diagnosis. In contrast, other trials used telephone or surveys to recruit patients and were only satisfied by patients' statements on their diagnosis without further investigations to confirm the diagnosis [31]. Three trials recruited patients with different types of CP condition. Then, these trials collectively analysed the results for all patients together regardless of their condition, while distinctions should have been made. Moreover, the duration of CP condition was considered neither as selective criteria nor as a confounding factor that might have affected the effectiveness of the drug under investigation [32].
of a drug, there is a need for trials of longer duration to test for long-
term efficacy as well as any potential chance for side-effects or abuse. 
Nevertheless, the duration in all selected trials ranged from 5 days to 6 
weeks. Moreover, the period varied across all trials without any 
standardized time interval determined to assess effectiveness. 15 of 21 
trials compared a cannabinoid to a placebo 3 compared cannabinoids to 
another drug and a placebo [34]. While 3 trials compared cannabinoid 
to other drugs without using a placebo or control group. A concern in 
the trials without placebo control is that it is impossible to be certain 
that any reported significant improvements are due to the drug under 
investigation since many trials report placebo response ranging from 
20 to 70%. Therefore, the reported results in the 3 trials could not be 
reliable unless there was a placebo control. 6 trials assessed the efficacy 
of smoked cannabis. In these trials, the study nurse explained the 
method of drug administration from an adjacent room and participants 
were then left to smoke without accurate calculation to the dose of the 
administered drug or close monitoring for the compliance with these 
instructions.

Moreover, dose titration protocols varied according to individual 
differences in sensitivity to the analgesic and adverse effects of cannabis; 
each participant titrated to the dose affording the maximum pain relief 
with the minimum adverse effects. The method of administration also 
varied from one trial to another; administration routes for cannabinoids 
included vaporization and mucosal sprays. Together, the various 
doses and ways of administration made the comparative analysis of 
cannabinoid efficacy very challenging.

Randomization

It was reported in all 21 trials suggesting a low risk of bias (Table 3). Nevertheless, the method used to generate the sequence of 
randomization or allocation was rarely reported or not well described 
in any of the trials.

Blinding

All trials were designed as double blinded trials. Blinding of both 
participants and observers was documented in all studies. However, 
the effectiveness of blinding was doubtful. At the end of the study, the 
subjects were asked to guess which group they had been designated 
for (experimental or control) as a means of estimating the success of 
blinding. In 8 trials, participants were able to correctly identify their 
group, suggesting ineffective participant blinding.

Results

In all 21 trials, participants were randomly assigned to the study 
groups and each group received intended treatment. Consequently, 
they were analysed for the primary (and secondary) outcome(s). Taken 
together, the 21 trials demonstrated a modest analgesic effect in pain 
as a primary outcome. In addition, 9 trials reported improvement in 
sleep. Drug-related adverse effects were generally described as well 
tolerated and most commonly included sedation, dizziness, dry mouth, 
nausea, and vomiting. Withdrawals potentially related to drug-related 
side effects was reported, however, it was minimal and did not seem to 
be associated with bias.

Outcomes

Conventionally in acute pain research, the response to a treatment 
is assessed by how much it reduces pain intensity; nevertheless, CP 
patients’ experience usually entails a range of serious implications, of 
which pain intensity is but one feature.

In all selected trials, the predominant outcome to be assessed, and 
therefore, the primary efficacy measure was not functional, emotional, 
or societal impact but pain intensity. All trials used various pain intensity 
cales as their primary outcome to assess the efficacy of cannabinoid 
on CP, ignoring other relevant outcomes to the condition under 
investigation. As a result, when all but one study, found a significant 
decrease in pain intensity related to cannabinoids administration, they 
concluded that cannabinoids were effective in managing CP compared 
to controls or other drugs. Hence, the determination of efficacy was 
mainly based on somewhat arbitrary rating scales that might not be 
clinically meaningful.

13 studies used other variables as secondary outcomes such as 
sleep, mood, anxiety, and depression, physical function and quality of 
life, the results for these outcomes were not clearly reported or nearly 
absent. Only 7 trials reported improvements in sleep, 5 trials showed 
improvements in quality of life. While 3 trials reported improvements 
in all measured outcomes. The variability in outcome measures, also, 
made it very difficult to evaluate and to conclude the real efficacy of 
cannabinoids.

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Table 3: Risk of Bias in selected trials.

= not reported, ≠ No, ✔️ = yes
Side effects and withdrawals
Patients' side effects were reported in all trials except for two neurocognitive adverse effects were reported as the most common (e.g., headache, dry mouth dysphoria, dizziness, and sedation). All reported side effects were generally described as well tolerated, and not leading to withdrawals. It is worthy to note, however, that as all selected RCTs were short-term trials and all used relatively small doses that could have masked potential severe side effects. Given the psychoactive properties of cannabinoids, several side-effects could be expected, including overdose, abuse, dependence, and even addiction. Additionally, as all drugs, cannabinoids can pose a toxic effect. However, end-organ failure secondary to medication was not assessed.

Withdrawals potentially related to drug-related side effects was reported, however, it was minimal and did not seem to be associated with bias. Although, these side-effects constituted from 3-18% of all participants, nevertheless, the majority of trials showed that lack or loss of effectiveness was the main reason for withdrawals.

Discussion
In reviewing RCTs investigating the efficacy of cannabinoids in managing CP different conditions, only 21 trials were found. There is a remarkable paucity in RCTs given the dramatic increase in cannabinoids use among CP patients. RCTs employed different methods and investigated various CP conditions. Despite discrepancies, all but one trial concluded that cannabinoids are effective in managing CP conditions, especially, neuropathic pain.

Implications for theory, research and clinical practice

Theory
In 1960, Ronald Melzak and Patrick Wall developed the gate control theory. Since then, the gate theory has been helping us understanding many of the complex pain conditions that we witness in practice. The theory shows that the experience of pain depends on a complex interplay of multiple factors, and pain sensation is the net result of the interactions between them. This new perception urges the research community to assess all factors affected by pain when assessing the efficacy of treatments. Eventually, there have been few tentative steps in this direction. Nevertheless, while research in cannabinoids is much better in this respect compared to opioids’ trials in CP; this new perspective is yet to be effectively translated to research methodologies.

Research
Cannabinoids are now increasingly used, more without prescription. Remarkably, previous systematic reviews have concluded that cannabinoids are effective in treating CP. What is surprising is that they were able to reach a conclusion, although the quality of RCTs were lacking. It seems that researchers are pressured to agree on relatively weak evidence just to follow the flow of use rather than waiting for more rigorous studies. It's, therefore, critical to efficiently assess the effectiveness of Cannabinoids. So far RCTs, conducted to assess the effectiveness of cannabinoids, have been associated with many limitations. The ambiguity of CP conditions, the discrepancies and variability in the methodology employed by RCTs were all confounding factors. The inclusion criteria of participants included in these trials were overwhelmingly different. Therefore, conclusions of these trials might be inappropriate to generalize or apply in clinical practice. As a result, this review cannot reach certainty regarding potential benefits as well as the serious side effects that may be associated with the use of cannabinoids for CP conditions on long-term basis. Nevertheless, “the absence of evidence of effect is not the same as the evidence of absence of effect”; i.e. not because there is no consistent evidence for the efficacy of cannabinoids in CP, this does not mean that they don't have any.

Researchers have the responsibility to provide evidence-based guidance on this important potential treatment. Additional trials need to be conducted in the future to further assess the risks and benefits of this potential drug, and to determine the most effective dose and the best method of administration. Future trials to determine the effectiveness of Cannabinoids for CP patients should be comprehensive focusing on risk-benefits assessments. Demographics of any RCT should be reported in details and in a more selective manner so that clinicians can determine how relevant the results to their patients. Researchers need to use a uniform method, beside the recommended IMMPACT outcomes to ensure standardization of pain research. The results of RCTs should be meaningful or clinically relevant to the same type of patients that resemble the participants that were studied.

Clinical practice
Owing to increasing public pressure, the Canadian government has set some regulations whereby cannabinoids can be obtained legally by prescription. However, clinicians have expressed concerns about the associated side effects.

Unfortunately, the absence of high-quality trials does not allow for consistent guidelines or recommendations for clinical practice use. The low quantity and quality of data available cannot provide real evidence to confirm efficacy or harm for routine clinical use. We can only say that Cannabinoids can be a potential treatment for CP; however, the same rules/precautions applied to opioids should be also employed with the Cannabinoids prescription. I think the decision on using Cannabinoids will remain as a one that is mainly based on the clinician’s experience as well as the patient's desire until evidence-based reports become available.

Conclusions
In conclusion, this review of 21 trials demonstrates that cannabinoids can be a potential treatment option for CP. Nevertheless, it was really challenging to conclude a definitive effectiveness for the cannabinoids since there were no standardized objective outcome tools to assess effectiveness in pain trials and because of the variable methods used.

Unfortunately, this paucity in research persists despite the dramatic increase in Cannabinoids use in many different forms between CP patients.

References