Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain

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ABSTRACT

Objective: Debilitating pain, occurring in 50–70% of multiple sclerosis (MS) patients, is poorly understood and infrequently studied. We summarized efficacy and safety data of cannabinoid-based drugs for neuropathic pain.

Data sources: Studies were identified from Medline, Embase, and Cochrane databases; Bayer Healthcare provided additional trials.

Study selection: Accepted were randomized, double-blinded placebo-controlled trials of cannabinoid-based treatments for MS-related/neuropathic pain in adults ≥ 18 years of age.

Data extraction: Two reviewers identified studies and extracted data; a third adjudicated disagreements. Data included baseline and endpoint pain scores on visual analog or 11-point ordinal scales.

Data synthesis: Of 18 articles and three randomized controlled trial (RCT) reports identified, 12 articles and two reports were rejected (9 = inappropriate disease or outcome, 1 = duplicate, 1 = review, and 1 = abstract); six accepted articles and one RCT-report involved 298 patients (222 treated, 76 placebo); four examined Sativex® (a cannabinoid/delta-9-tetrahydrocannabinol (THC) buccal spray) (observations = 196), five cannabidiol (n = 41), and three dronabinol (n = 91). Homogeneity χ² values were non-significant, allowing data combination. Analyses focused on baseline-endpoint score differences. The cannabidiol/THC buccal spray decreased pain 1.7 ± 0.7 points (p = 0.018), cannabidiol 1.5 ± 0.7 (p = 0.044), dronabinol 1.5 ± 0.6 (p = 0.013), and all cannabinoids pooled together 1.6 ± 0.4 (p < 0.001). Placebo baseline-endpoint scores did not differ (0.8 ± 0.4 points, p = 0.023). At endpoint, cannabinoids were superior to placebo by 0.8 ± 0.3 points (p = 0.029). Dizziness was the most commonly observed adverse event in the cannabidiol/THC buccal spray arms (39 ± 16%), across all cannabinoid treatments (32.5 ± 16%) as well as in the placebo arms (10 ± 4%).

Conclusion: Cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in MS.

Limitations: This review was based on a small number of trials and patients. Pain related to MS was assumed to be similar to neuropathic pain.

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Introduction

Multiple sclerosis (MS) is an unpredictable, common neurologic disease of the central nervous system, including the brain and spinal cord. The disease attacks the protective myelin covering of the central nervous system, causing inflammation and often destroying the myelin in patches. The severity of MS, progression and specific symptoms cannot be predicted at the time of diagnosis. There are four forms of MS: relapsing–remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and progressive relapsing (PRMS).

An estimated 50,000 Canadians have MS. Prevalence rates range from one MS case per 500 people to one in 1000 across the country. Canada is a high risk area for the disease, which occurs more often in countries further away from the equator. Each day in this country, nearly three more people are diagnosed with MS out of a population of about 32.5 million.

In 1998, the Canadian Burden of Illness Study Group assessed the cost of MS from the Canadian societal perspective. In that study, data were collected from a total of 198 patients, of whom 62 had mild, 68 had moderate, and 68 had severe disease. They estimated that the annualized societal costs (CAD) per patient were $14,523 for patients with the mild, $21,698 for the moderate, and $37,024 for the severe forms of the disease. Further studies have been performed in other industrialized nations. For example, similar work has been executed in Italy by Amato and colleagues, in the USA by Whetten-Goldstein and associates, and in Sweden by Henriksson and coworkers. Reviews have been published by Miltenburger and Kobelt and by Grudzinski et al. All of these authors concluded that MS is very costly to the individual, health care system, and society and all recommended further research.

MS is one of the most studied neurological diseases; however, scant attention has been placed on symptomatic therapy, especially in the treatment of the associated pain. Pain can occur as a consequence of neurological impairment and disability, or because of neurological damage. Disability due to pain may be more important than previously recognized for the MS population. Approximately 25% of the subjects in a study performed by Ehde and others described having a chronic pain problem characterized by severe intensity and which caused substantial interference with daily activities.

The number of patients having MS who suffer from pain is high, but the exact rate is unknown. Estimates vary widely from 10% to 80%, with an average of about 50%. In an examination of 665 patients in Italy, Brichetto and colleagues found that the most commonly treated MS symptoms were pain (28%) and spasticity (27%). The incidence of pain has no apparent correlation to disease severity and, so far, no evidence has shown that pain occurs more frequently in any particular disease subtype. Moreover, a comprehensive definition of pain has not been established, thus causing difficulties in the evaluation of this chronic, evolving symptom.

Current pain treatments are unable to meet the objectives of pain management in MS. New therapeutic strategies are now becoming available and interest in the symptomatic treatment of MS is growing. Therefore, a need exists to examine the evidence in the published literature in order to quantify the benefits and risks of currently available treatments for pain in MS.

One of the advances in treating pain has been the introduction of extracts of cannabis. Active drugs include cannabidiol, dronabinol (also known as tetrahydrocannabinol or THC), and a 1:1 mixture of the other two drugs in Sativex* (a cannabidiol/delta-9-tetrahydrocannabinol (THC) buccal spray). These products provide an option for patients whose pain is not ameliorated by traditional drugs. Although a number of reviews of the topic have been published, no quantitative summary of their effects in treating neuropathic pain, such as that from MS, has yet been published. The purpose of the present study was to address that void. Our aim was to undertake an evidence based review to quantify the effect of cannabis based drugs in the management of pain related to MS or comparable neuropathic pain syndromes.

Methods

We attempted to obtain all randomized, double-blinded, placebo controlled trials involving the use of cannabis-based drugs in the treatment of pain associated with MS or comparable neuropathic pain in adults ≥ 18 years of age. We assumed neuropathic pain to be comparable to MS related pain; hence we included all studies of cannabinoids in neuropathic pain. Only full peer reviewed articles were accepted; abstracts from proceedings or professional meetings were not considered. In order to meet inclusion criteria, trials were required to have examined at least one active treatment either against itself (e.g., different doses, dosage forms, or administration times, etc.), or against another active drug, and/or against placebo. There were no restrictions on language or year of publication. The clinical outcome of primary interest was the pain score obtained from

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a 10 cm long visual analog scale (VAS) or equivalent [e.g., 11-point scale such as the Box Scale (BS-11)]. We accepted all durations of drug administration.

Two independent reviewers searched Medline, Embase, Cochrane, and HealthSTAR databases from inception to the end of June 2006. We also hand searched the references of all articles retrieved and from reviews of the topic. Bayer provided additional unpublished studies. The reviewers assessed identified studies for inclusion against preset criteria, with discrepancies adjudicated by a third reviewer.

Data were extracted onto a pre-designed form by two extractors, with outcomes verified by a third person. Data extracted included the number of study participants, duration of study, dropouts due to adverse events, lack of efficacy, or other reasons, numbers of patients completing the study, baseline scores on all pain scales and their standard deviations (SDs), as well as endpoint scores and SDs, and reported rates of adverse events (AEs).

As a first step in determining data combinability, we calculated $\chi^2$ values for homogeneity of effects. We also calculated the $I^2$ value which determined the proportion of between-study variance that is due to study variation, as opposed to background variation (i.e., chance). To examine publication bias, we created funnel plots and calculated the Begg–Mazumdar statistic.

To analyze treatment efficacy, we used as our primary measure the difference on the VAS (or equivalent scale) between baseline and endpoint values. In that way, we could quantify the effect on pain reduction of both the active drug and placebo. Data from individual studies were combined using a random effects model, which allows for more weight to be given to larger studies. As well, it incorporates between-study variance into the calculations. The outcome of interest was the weighted overall difference between baseline and endpoint expressed in points from the 0–10 scale, along with a standard error. We calculated these results for each of the three available cannabinoids (i.e., the

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**Figure 1. Literature search tree**

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cannabidiol/THC buccal spray, cannabidiol, and dronabinol), and for placebo.

Rates of AEs were combined for each drug and/or placebo using a random effects meta-analytic approach across all study arms. A 95% confidence interval is also presented for each corresponding meta-analytic rate. Where only one study reported adverse events, the score method was used to determine the confidence interval.

Rates were compared for each drug, all active drugs combined, and for placebo between endpoint and baseline. Active drugs were also compared against placebo at baseline and at endpoint.

The quality of all papers was also examined. Two evaluators independently assessed each clinical trial using Jadad criteria. Jadad et al. developed a scale to evaluate the quality of clinical reports in pain relief. Articles could score from 0 to 5, with scores of 0, 1, and 2 considered poor and scores of 3, 4, or 5 considered good. Differences in scoring were resolved using consensus discussion.

### Results

We originally identified 343 possible studies. Figure 1 summarizes the literature search results. After reading titles, 290 were rejected as being not applicable. We retrieved 21 full reports, including 18 published articles plus three studies supplied by the company. Of the three reports, two were also published and had already been included. The remaining trial was also included in the meta-analysis as it was undergoing peer review. Of the other 18, 12 were rejected: eight of them had inappropriate disease or outcome, two were duplicates, one was a review, and one was in abstract form.

Therefore, we were able to use data from six papers and one RCT report that involved 298 unique patients, including 222 treated with cannabis preparations (many of whom also crossed over to placebo) and 76 receiving only placebo. It should be noted that, because many of the trials involved crossovers (often to multiple therapies), the numbers of observations often do not match the number of patients. For example, Karst examined the same patients under four different sets of conditions. Across all studies, there were six trials of the cannabidiol/THC buccal spray (with 196 observations), five cannabidiol (n = 41), three dronabinol (n = 91) for a total of 328 pairs of patient outcome measurements (the pairs being baseline and endpoint scores).

Table 1 summarizes those studies and their baseline characteristics. Some articles, including both cannabidiol papers, provided several trial arms with active drugs. One cannabidiol paper also included arms which were usable for the cannabidiol/THC buccal spray and dronabinol analyses.

When scored according to the Jadad criteria, the quality of all of the papers included for data extraction was rated as ‘good’. Five papers scored the maximum of 5 points, one scored 4 and the other 3. The average was 4.6, which would be considered very good quality overall.

With regards to homogeneity testing, the chi square values in all analyses were non-significant (p > 0.05), indicating a lack of heterogeneity among the studies within each analysis. As well, all I² values were zero, also indicating no issue with between-study variance. Given these results, data from all cannabis trials were considered to be combinable.

The funnel plots (not shown) did not display a lack of small, non-significant studies, which would denote the presence of bias. The Beg–Mazumdar test was also non-significant; for placebos, Kendall’s tau was 0.449 (p = 0.072) and for the cannabis preparations, tau was

### Table 1. Characteristics of randomized placebo-controlled studies included in this analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>First author</th>
<th>Instrument/scale</th>
<th>Baseline, n</th>
<th>Treatment duration</th>
<th>Average age</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabidiol/THC</td>
<td>Berman</td>
<td>BS-11</td>
<td>48</td>
<td>14–20 days</td>
<td>39.0</td>
<td>5</td>
</tr>
<tr>
<td>buccal spray</td>
<td></td>
<td></td>
<td>48*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>Dempster</td>
<td>BS-11</td>
<td>36</td>
<td>3 weeks</td>
<td>54.6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Rog</td>
<td>BS-11</td>
<td>34</td>
<td>4 weeks</td>
<td>49.2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Wade</td>
<td>100 mm VAS</td>
<td>80</td>
<td>6 weeks</td>
<td>50.5</td>
<td>5</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Karst</td>
<td>VAS</td>
<td>21</td>
<td>1 week</td>
<td>51.0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Wade</td>
<td>11-point ordinal</td>
<td>24</td>
<td>2 weeks</td>
<td>48.0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Svendsen</td>
<td>11-point ordinal</td>
<td>24</td>
<td>6 weeks</td>
<td>50.0†</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>267</td>
<td></td>
<td>263</td>
<td></td>
</tr>
<tr>
<td>Unique patients</td>
<td></td>
<td></td>
<td>298</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Crossover study
†Reported median age
0.297 (p = 0.139). Therefore, publication bias was not deemed to be present to a great extent.

Table 2 presents the efficacy results from all of the randomized controlled trials that were included in the analysis. There was no difference (p = 0.822) between baseline pain scores of patients receiving cannabinoids (6.2 ± 0.4) and those receiving placebo (6.4 ± 0.4). All of the active drugs produced endpoint-baseline score reductions that were in excess of 1.5 points on the 11-point scale and all were statistically significant. At endpoint, cannabis preparations were superior to placebo, with a difference in effect size of 0.8 point (p = 0.029).

Placebo reduced pain scores an average of 0.8 points, which was significantly different from zero (p = 0.023). However, it was noted that two of the studies allowed patients to freely use rescue medications.35,36 Removing those studies lowered the placebo effect to 0.6 point, which was not significantly different from zero (p = 0.170).

Reported meta-analytic rates and corresponding confidence intervals of adverse events are presented in Table 3. Dizziness was the most commonly observed adverse event across all cannabinoid agents, reported by 35% of the patients. The most commonly observed adverse event for the placebo arms was also dizziness, reported in 10.1% of the patients. In studies of the cannabidiol/THC buccal spray, 39% of patients reported dizziness. Withdrawals due to adverse events were virtually identical, occurring in 5.5% (14/255) of patients receiving cannabis and 5.1% (13/253) of those treated with placebo.

**Discussion**

The number of papers that addressed the topic of this research was not large. Nonetheless, we have quantified the available literature and summarized the relevant clinical rates. As more studies are performed, these rates may be adjusted and refined until a stable estimate is produced.

We found that cannabinoids seem to have a good effect, consistently lowering pain scores from baseline. However, these scores require clinical interpretation. Farrar et al. tested several scales measuring pain outcomes to determine what constituted a relevant change in pain intensity or severity. They concluded that a reduction of 2 points on a 0–10 scale would be the optimal cut-off point to clearly indicate a clinically relevant response. They noted that this amount of absolute change yielded the best combination of sensitivity (73.9%), specificity (81.0%) and accuracy (69.9%) on all of the scales that they tested.

However, they only tested discrete values. A reduction of one point was associated with 95.3% sensitivity, 31.6% specificity, and 77.4% accuracy. A linear interpolation reveals that a difference of 1.4 points would yield a specificity of about 50%, with both sensitivity and accuracy > 70%. Similarly, 1.6 points provides 60% specificity and 1.9 gives 70% (all others remain > 70%). Therefore, the true threshold would lie somewhere between 1.4 and 1.9 points on a visual analog scale (or when considering group averages), depending on the level of specificity that would be tolerated. In the present case, specificity would be of lesser importance, since the patients are measuring their own pain relief. Therefore, if we use a reduction of 2 points in pain intensity on analog scales as a clinically relevant measure and 1.5 to indicate the minimum detectable difference for pain relief, then cannabinoids would all be considered efficacious for these types of patients. In all cases, a 2-point difference lies within one standard error of the group mean (e.g., all cannabinoids: 1.6 ± 0.4). Thus, all drugs in this class, and cannabinoids as a group, come very close to meeting the higher criterion and all surpass the minimum. Furthermore, a subgroup analysis of trials of the cannabidiol/THC buccal spray of 6–10 weeks yielded an effect size of 2.6 points.

But there is another aspect to consider. The trial by Zajicek and coworkers was rejected from this analysis because it did not use an 11-point scale to measure pain. They used a 3-category scale of response, no change, or deterioration. After two different sets of patients received cannabis extract (i.e., the cannabidiol/THC buccal spray), 46% of 148 reported a reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trials</th>
<th>Patients</th>
<th>Difference from baseline*</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabidiol/THC buccal spray</td>
<td>6</td>
<td>196</td>
<td>1.7</td>
<td>0.7</td>
<td>0.018</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>5</td>
<td>41</td>
<td>1.5</td>
<td>0.7</td>
<td>0.044</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>3</td>
<td>91</td>
<td>1.5</td>
<td>0.6</td>
<td>0.013</td>
</tr>
<tr>
<td>All cannabinoids</td>
<td>14</td>
<td>328</td>
<td>1.6</td>
<td>0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>10</td>
<td>250</td>
<td>0.8</td>
<td>0.4</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*Scores recorded on an 11-point scale, with 0 being no pain and 10 being the worst imaginable.
in pain scores (which was not qualified any further) as did 50% of 128 given δ-9-THC, as opposed to only 30% of 140 who were given placebo \( (p = 0.002) \). The remainder scored the same or worse than baseline, as would be expected in an untreated population. It may be that, like placebo responders, there are cannabis responders. Cannabis receptors in the human brain are well known\(^44\). Perhaps some patients respond better than others to drugs affecting these receptors. If that suggestion is correct, then cannabis would be very effective if the analysis would be restricted to responders. They would then have about twice the pain relief that we found across the entire group (that is, the numerator would remain the same, but the denominator would be reduced by half). At the same time, there would be little or no impact on non-responders, who would refrain from using these drugs. In other words, when the drug works, it works very well, and when it does not work, there is no effect at all. In any event, our estimates must be considered conservative.

The finding of a reduction of 0.8 points for placebo must be assessed with care. It should be noted that, in those trials, patients in the placebo group were allowed to receive rescue drugs for pain and were allowed to increase the doses of those pain drugs. For example, in the Rog study\(^{31,42}\), 45% of patients were given analgesics as rescue medication to get through the day. As well, in those trials, there was a great deal of dizziness reported as an adverse effect. In the cannabidiol/THC buccal spray group, there was no difference in pain response between the ‘dizzy’ and ‘not dizzy’ groups, however, in the placebo group, it was noted that patients who reported dizziness also reported lower pain scores. It could be that these patients presumed that they were receiving the active drug, which is known to produce dizziness. Therefore, the overall effect reflects not only that of placebo, but also that of the rescue medications. As mentioned above, when we removed the two studies in which patients were freely allowed to use rescue medication\(^{37,41}\), the effect size decreased and was non-significant. In any event, we do expect some placebo responders in all pain trials.

The analgesic response to cannabinoids seems to be retained over time, at least for the 6–10 week follow-up period. No studies were found that examined longer time periods, except for the two studies by Zajicek\(^{38,39}\). As mentioned, those researchers did not use an 11-point scale to measure pain, so no further comparisons could be made. Since these conditions are chronic and impact substantially upon patients’ quality of life, future research should be directed toward determining the maximal duration of this effect, and evaluate whether tolerance develops over time.

### Table 3. Meta-analytic rates with 95% confidence intervals of reported adverse events

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total studies</th>
<th>Total patients</th>
<th>Withdrawals</th>
<th>Dizziness</th>
<th>Somnolence</th>
<th>Headache</th>
<th>Nausea</th>
<th>Diarrhea</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabidiol/THC</td>
<td>4</td>
<td>197</td>
<td>0.038 ± 0.027</td>
<td>0.300 ± 0.163</td>
<td>0.651 ± 0.073</td>
<td>0.042 ± 0.016</td>
<td>0.070 ± 0.051</td>
<td>0.080 ± 0.078</td>
<td>0.070 ± 0.056</td>
</tr>
<tr>
<td>Buccal spray</td>
<td>2</td>
<td>74</td>
<td>0.017 ± 0.110</td>
<td>0.583 ± 0.172</td>
<td>0.417 ± 0.095</td>
<td>0.250 ± 0.149</td>
<td>0.137 ± 0.272</td>
<td>0.056 ± 0.039</td>
<td>0.013 ± 0.066</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>1</td>
<td>24</td>
<td>0.043 ± 0.029</td>
<td>0.325 ± 0.164</td>
<td>0.123 ± 0.077</td>
<td>0.050 ± 0.039</td>
<td>0.050 ± 0.039</td>
<td>0.065 ± 0.059</td>
<td>0.061 ± 0.030</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>1</td>
<td>7</td>
<td>0.026 ± 0.023</td>
<td>0.101 ± 0.038</td>
<td>0.055 ± 0.026</td>
<td>0.050 ± 0.059</td>
<td>0.050 ± 0.059</td>
<td>0.065 ± 0.059</td>
<td>0.061 ± 0.030</td>
</tr>
<tr>
<td>All cannabinoids</td>
<td>7</td>
<td>253</td>
<td>0.036 ± 0.023</td>
<td>0.101 ± 0.038</td>
<td>0.055 ± 0.026</td>
<td>0.050 ± 0.059</td>
<td>0.050 ± 0.059</td>
<td>0.065 ± 0.059</td>
<td>0.061 ± 0.030</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>253</td>
<td>0.036 ± 0.023</td>
<td>0.101 ± 0.038</td>
<td>0.055 ± 0.026</td>
<td>0.050 ± 0.059</td>
<td>0.050 ± 0.059</td>
<td>0.065 ± 0.059</td>
<td>0.061 ± 0.030</td>
</tr>
</tbody>
</table>

*3 studies reporting
†5 studies reporting
‡5 studies reporting
§2 studies reporting
**4 studies reporting
¶6 studies reporting
The major limitation of this evidence based review was the small number of trials (i.e., seven) and patients (i.e., 298 unique patients). Another limitation was the assumption that pain in MS and any neuropathic pain would be affected in the same manner. Although all studies involving the cannabidiol/THC buccal spray were for pain in MS, more MS-related studies are needed for this and other pain indications.

Conclusion

Cannabinoids are associated with a clinically relevant and statistically significant lowering of pain scores. Some patients do not obtain relief, but others respond very well. A need exists for further studies of clinical outcomes of pain in MS. Economic implications should also be examined.

Acknowledgment

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