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

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CRD summary

The review concluded that cannabinoids, including the cannabidiol/delta-9-tetrahydrocannabinol buccal spray, are effective in treating neuropathic pain in patients with multiple sclerosis. However, given the limitations of the evidence presented, the reliability of the authors' conclusions is uncertain.

Authors' objectives

To evaluate the effectiveness and safety of cannabis-based drugs in pain management related to multiple sclerosis (MS) or comparable neuropathic pain syndromes.

Searching

MEDLINE, EMBASE, the Cochrane CENTRAL Register and HealthSTAR were searched from inception to the end of June 2006. The reference lists of retrieved studies and from reviews on the topic were handsearched. Additional unpublished data were sourced from a drug manufacturer (Bayer). Abstracts were not included. No language restrictions were applied.

Study selection

Study designs of evaluations included in the review

Randomised, double-blinded, placebo-controlled trials were eligible for inclusion.

Specific interventions included in the review

Studies of the use of cannabis-based drugs for the treatment of pain associated with MS or comparable neuropathic pain in adults were eligible for inclusion. To be included, trials needed to have assessed at least one active treatment against either itself (e.g. different doses, dosage forms or times of administration) or against another active drug, and/or against placebo. All durations of drug administration were eligible for inclusion. The included studies evaluated cannabidiol in conjunction with a delta-9-tetrahydrocannabinol (THC) buccal spray, cannabidiol alone, or dronabinol alone in comparison with placebo. The duration of treatment ranged from 1 to 6 weeks.

Participants included in the review

Studies of adult patients aged 18 years or older who were receiving treatments for MS-associated pain or comparable neuropathic pain were eligible for inclusion. At least two of the included studies assessed general neuropathic pain rather than pain associated with MS. The average age of participants in the included studies ranged from 39 to 54.6 years.

Outcomes assessed in the review

Studies assessing pain score obtained from a visual analogue scale (VAS) or equivalent such as the Box Scale (BS-11) were eligible for inclusion. The included studies assessed pain using the BS-11 scale, VAS scale, a 100-mm VAS scale, or an 11-point ordinal scale. Scores on an 11-point scale ranged from 0 (no pain) to 10 (worst pain imaginable).

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed studies for relevance, with any disagreements adjudicated by a third reviewer.

Assessment of study quality

The quality of the studies was assessed using the Jadad scale, which has a maximum score of 5; studies scoring 0 to 2 are rated poor, while studies scoring 3 to 5 are rated good. Two reviewers independently assessed validity and resolved any disagreements through discussion.

Data extraction

Two reviewers independently extracted the data onto a pre-designed form and resolved any disagreements through consensus, with outcomes verified by a third reviewer where required. Data on the mean pain scores, and standard deviations, at baseline and at the end of the trial in each group were extracted and used to derive the standardised mean difference (SMD) and its standard error (SE) relative to baseline and to placebo.

Methods of synthesis

How were the studies combined?

The results of individual studies were combined using a random-effects model to produce a weighted SMD (effect size). Rates of adverse events were compared for each drug, all active drugs combined and for placebo between end point and baseline. Active drugs were compared against placebo at baseline and end point. Publication bias was assessed using funnel plots and the Begg-Mazumdar statistical test.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared and I-squared tests.

Results of the review

Seven RCTs (298 unique patients: 222 treated with cannabis preparations (many of whom also crossed over to placebo) and 76 treated with placebo alone) were included. Four of these were crossover trials.

The quality of all 7 included studies was rated as good. Five studies scored 5, one scored 4 and one scored 3. Both the chi-squared and I-squared statistical tests indicated that there was no significant statistical heterogeneity between the studies. The Begg-Mazumdar test showed no evidence of publication bias.

There were no statistical differences at baseline between pain scores of patients treated with cannabinoids and those receiving placebo.

Cannabis preparations were more effective in reducing pain scores than placebo for the treatment of MS-related or neuropathic pain, with a difference in effect size of 0.8 points; the difference was statistically significant (p=0.029). The difference from baseline was 1.7 (SE 0.7, p=0.018) for cannabidiol/THC buccal spray (6 studies, n=196), 1.5 (SE 0.7, p=0.044) for cannabidiol alone (5 studies, n=41), 1.5 (SE 0.6, p=0.013) for dronabinol (3 studies, n=91) and 1.6 (SE 0.4, p<0.001) for all cannabinoids (14 trial arms, n=328).

Data for placebo groups (10 studies, n=250) reported an average reduction in pain scores of 0.8 points, which was statistically significant (p=0.023). A post hoc analysis removing 2 studies that allowed free use of ‘rescue’ medications, including analgesics, lowered the placebo effect to 0.6 points, which was not statistically significant.

Dizziness was the most commonly reported adverse event for all cannabinoid treatments (32.5% +/- 16.4) and for placebo (10.1% +/- 3.8). In studies of cannabidiol/THC buccal spray, 39% (+/- 16.3) reported dizziness.

Withdrawals due to adverse events were similar between patients receiving cannabis (5.5%, 14 out of 255) and those treated with placebo (5.1%, 13 out of 253).

Authors' conclusions

Cannabinoids are associated with a clinically relevant and statistically significant lowering of pain scores. Some patients did not experience pain relief but others responded well.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to locate unpublished studies. No language restrictions were applied and abstracts were excluded. No evidence of publication bias was found. No search terms were reported so it is not possible to either evaluate or replicate the searches. Methods were used to minimise error and bias in the study selection, validity assessment and data extraction processes. The analysis comparing changes from baseline and effectiveness relative to placebo was not clearly established. In addition, the clinical significance of the observed effects was unclear. The authors also made assumptions about the generalisability between pain in MS and

neuropathic pain in other conditions. The included studies had small sample sizes and were of short-term treatment (the longest lasted 6 weeks), and this also should be considered when interpreting the results. Given the limitations of the evidence presented, the reliability of the authors' conclusions is uncertain.

The review was funded by Bayer Inc., which markets the cannabidiol/THC buccal spray in Canada.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research evaluating longer term clinical outcomes of cannabinoid treatment for pain in MS is needed. In addition, economic implications should also be assessed.

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