A systematic review of pharmacological pain management in multiple sclerosis

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CRD summary
This review concluded that anticonvulsants and off-label use of dextromethorphan/quinidine were identified as promising treatments for chronic pain in multiple sclerosis but that the evidence was insufficient to establish how to choose optimal therapy for particular patients. Limitations of the evidence and reporting in the review mean that the conclusions regarding anticonvulsants and dextromethorphan/quinidine may not be reliable; the part of the conclusion regarding optimal therapy appears appropriate because it reflects the paucity of the evidence presented.

Authors' objectives
To review pain management strategies for the reduction of non-spastic and non-trigeminal neuralgic pain in multiple sclerosis patients.

Searching
PubMed, CINAHL, Science Citation Index Expanded, Conference Proceedings Citation Index-Science and ClinicalTrials.gov were searched for articles written in English. PubMed was searched to November 2012. The other databases were searched to December 2012. Search terms were reported. Reference lists of reviews and studies citing the reviews were searched manually.

Study selection
Eligible studies were experimental studies that evaluated the effects of pharmacological pain management interventions in adults (≥18 years) with clinical diagnoses of multiple sclerosis. Study populations had to have been diagnosed using standardised criteria and patient-reported pain had to have been measured using a validated tool (examples provided in the review). Studies with mixed populations of spastic/trigeminal neuralgic patients and multiple sclerosis patients who were experiencing other types of pain were included. Studies were excluded if patient-reported pain was mentioned as an adverse event.

The included studies were carried out in North America, the Middle East and Europe (including one UK-based study). Where reported, many studies were sponsored by major pharmaceutical companies. Major classes of pharmacological interventions included anticonvulsants, anti-depressants, cannabinoids, dextromethorphan/quinidine and opioids/opioid antagonists; drugs and regimens varied. A small proportion of the studies allowed concomitant use of pain medications. Most studies assessed patient-reported pain as the primary outcome. Mean age of participants ranged from 32 to 55 years; the proportion of men per study ranged from 17% to 43%. Where reported, treatment duration ranged from 20 minutes to 14 weeks. Participant eligibility criteria varied across the studies. Where studies reported comparator treatments, these consisted of a type of placebo (such as a form of oromucosal spray, tablets/capsules) or use of transcutaneous electrical nerve stimulation (TENS). Mean duration of multiple sclerosis prior to enrolment ranged from seven to 20 years (where reported).

Two reviewers independently screened studies for inclusion in the review; any disagreements were resolved by consensus involving a third reviewer.

Assessment of study quality
Study quality was assessed according to Cochrane Collaboration criteria for randomisation, allocation concealment, clear definition of primary outcome, inclusion/exclusion criteria, baseline comparability of groups and blinding of participants, personnel and outcome assessors. Levels of evidence for individual studies were classified into four classes (Class 1 indicated the strongest level of evidence and Class 4 indicated the weakest) using criteria from the American Academy of Neurology.

Two reviewers independently assessed study quality.

Data extraction
Data on patient-reported pain (mean scores and standard deviation values) were extracted to calculate mean...
differences within and between groups and where possible estimate Cohen’s d effect sizes and 95% confidence intervals. Where standard deviation values were not reported or calculable, differences between scores were recorded.

The authors did not report how many reviewers extracted these data.

Methods of synthesis
When at least three studies were available from the same treatment class, effect sizes and 95% confidence intervals were pooled using a random-effects model. Any remaining data were synthesised narratively in sub-sections for each treatment class; within these sub-sections studies were also separated according to the class of evidence they had been assigned.

Results of the review
Fifteen trials were included in the review (number of participants unclear): seven had control groups, five had a crossover design and three did not have control groups. Four studies were classified as Class 1 evidence, one as Class 2 evidence, six as Class 3 evidence and four as Class 4 evidence. A full breakdown of the results was provided in the review paper.

Anticonvulsants (six trials: one with Class 1 evidence, two with Class 3 evidence and three with Class 4 evidence): A statistically significant greater reduction in pain scores was observed in anticonvulsant treatment groups versus comparator groups (pooled Cohen’s d -1.88, 95% CI -3.13 to -0.64; four trials; 78 participants).

Cannabinoids (four trials: two with Class 1 evidence and two with Class 3 evidence): No statistically significant differences in pain scores were observed between cannabinoid treatment groups and comparator groups (pooled Cohen’s d 0.08, 95% CI -0.74 to 0.89; three trials; 565 participants).

Other pharmacological interventions (five trials): Mixed results for pain reduction were found with use of antidepressants (two trials: one with Class 1 evidence and one with Class 3 evidence). One trial with Class 1 evidence found an improvement in pain reduction with the use of dextromethorphan/quinidine compared with placebo (Cohen’s d 0.22). Two placebo-controlled crossover trials (one with Class 3 evidence and one with Class 4 evidence) each showed reductions in pain with the use of the opioid antagonist naltrexone (mean score difference between groups -2.13) and the opioid agonist morphine (Cohen’s d -0.48).

In the four trials with Class 1 evidence, dizziness, nausea and somnolence were the most commonly reported adverse events. Further results (including data on adverse events per drug type) were reported in the review paper.

Authors’ conclusions
Anticonvulsants and off-label use of dextromethorphan/quinidine were identified as being promising treatments for chronic pain in multiple sclerosis. The evidence was insufficient to establish how to choose optimal therapy for particular patients.

CRD commentary
The review question and inclusion criteria were clearly defined. A range of data sources were accessed and attempts were made to locate unpublished literature. The restriction to studies in English meant that some relevant studies may have been missed. The review processes of study selection and quality assessment were performed in duplicate; it was unclear whether this was also the case for data extraction so the presence of reviewer error/bias could not be ruled out.

Suitable quality assessment criteria were employed. Study quality was variable. Most studies were classified as providing Class 3 or 4 evidence (weaker evidence). Differences between the studies meant that the predominantly narrative form of synthesis was appropriate. This was further supported by the fact that the evidence for each treatment class consisted only of a small number of studies with short durations and an unclear number of participants. Where pooled analyses were conducted, statistical heterogeneity values and/or forest plots were not presented so it was difficult to judge whether any individual studies may have influenced the overall result. Two of the pooled analyses did not include all of the studies described for the treatment class and the reason for this was unclear. The authors acknowledged that the uncontrolled studies included in this review may reflect an overestimation of the true treatment effect.
Limitations of the evidence and reporting in the review mean that the conclusions regarding anticonvulsants and dextromethorphan/quinidine may not be reliable; the part of the conclusion regarding optimal therapy appears appropriate because it reflects the paucity of the evidence presented. The recommendation for longer-term assessment of the pharmacological treatments appears justified.

**Implications of the review for practice and research**

**Practice:** The authors stated that the risks and benefits of nabiximols and dextromethorphan/quinidine need to be carefully considered before clinicians prescribe them. In the absence of evidence, clinicians and patients need to carefully consider treatment regimens with regards to efficacy, risk of adverse events, cost and clinical complexity of the patient (for example, co-morbid conditions and concomitant medication use).

**Research:** The authors stated that long-term assessment of the efficacy and safety of pharmacological treatments for pain in multiple sclerosis patients was needed.

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