Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review

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Authors' objectives
To systematically review the published evidence available relating to the clinical efficacy of oral treatments for spasticity in multiple sclerosis (MS).

Searching
The following electronic databases were searched in June and July 2000 (dates not restricted): MEDLINE, EMBASE, the Science Citation Index, the Cochrane Database of Systematic Reviews, the CENTRAL/CCTR database in the Cochrane Library, PubMed, HealthSTAR, Best Evidence, CINAHL, AMED, and the NHS Centre for Reviews and Dissemination (DARE, NHS EED, and HTA). Studies not retrieved through the database searches, such as current research and grey literature, were also sought. In addition, the National Research Register, MRC Clinical Trials Register and the US National Institutes of Health Clinical Trials register were searched, and the publication lists and current research registers of health technology assessment and guidelines-producing agencies, and funding and regulatory bodies were consulted. The search results were restricted to articles in the English language.

Study selection

Study designs of evaluations included in the review
The a priori inclusion criteria relating to study design were not clear. The actual studies included in the review were randomised controlled trials (RCTs) and a controlled trial.

Specific interventions included in the review
Studies of oral treatments for spasticity were eligible for inclusion. Cannabinoids were excluded. The treatments investigated by the included studies were baclofen, dantrolene, tizanidine, diazepam, gabapentin and threonine. The comparators included other oral treatments for spasticity or placebo. The length of time on treatment ranged from 2 days to 15 weeks.

Participants included in the review
Studies of patients with MS were eligible for inclusion. At least 50% of the trial participants were required to have MS, or if fewer than 50% of participants had MS, then the findings for patients with MS were required to be presented separately.

Outcomes assessed in the review
Studies reporting clearly defined clinical or functional outcomes were eligible for inclusion. There was considerable variation in the outcome measures used in the included studies, and in some cases different studies used the same outcome measure in different ways.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The validity of the included studies was assessed using the Jadad scale. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The data were extracted by one reviewer and checked by another.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a qualitative analysis.

How were differences between studies investigated?
The authors inspected study details for heterogeneity.

**Results of the review**
A total of 22 studies (n=1,200) met the inclusion criteria: 21 RCTS (n=1,181) and 1 controlled trial (n=19). The numbers given are total numbers of participants, as opposed to numbers of participants with MS.

Baclofen (6 RCTs and 1 controlled trial).

The Jadad scores ranged from 2 to 4 out of a possible 5.

In two of the five studies comparing baclofen with placebo, statistically significantly more patients improved when on baclofen than on placebo; the other three studies (that used the lowest maximum dose) showed no statistically-significant difference. Neither of the comparisons between baclofen and diazepam showed a statistically-significant difference. Side-effects were common. Those most commonly reported were drowsiness, weakness, paresthesia and dry mouth. The side-effects appeared to limit the dose tolerated, but were fewer and more readily tolerated than those caused by diazepam.

Dantrolene (3 RCTs).

There were two Jadad scores of 3 and one of 2 out of 5. There were no consistent differences between dantrolene and placebo (2 RCTs) or dantrolene and diazepam (1 RCT). Commonly reported side-effects included weakness, light-headedness, dizziness, nausea and diarrhoea.

Tizanidine (8 RCTs with 10 comparisons). Two studies scored 2 out of 5 for validity, while the others scored 3 or more out of 5.

In comparison with placebo, the single-dose showed a statistically-significant, dose-dependent improvement in the pendulum test. One smaller crossover study of 4-week duration, in which only two thirds of the patients had MS, reported significantly more patients (as measured using the Ashworth score) on tizanidine than on placebo. One of the two longer term studies comparing tizanidine with placebo showed a reduction in muscle tone on tizanidine that was significantly greater than placebo, while the other did not. Neither of these studies demonstrated any difference in functional status between the placebo and treatment groups. Four studies compared tizanidine to baclofen. Overall, there was no difference between the two drugs on any of the outcomes assessed. One study compared tizanidine with diazepam in MS patients. Overall, there was no difference between the drugs. In terms of side-effects, overall, tizanidine was well tolerated. The most frequent side-effects mentioned were drowsiness and a dry mouth.

Diazepam (4 RCTs).

All studies scored 3 out of 5 for validity. There was no difference between the two drugs in any of the studies for any of the measures used. In every case, diazepam caused significantly more side-effects than the comparator drug. The most commonly reported side-effects were sedation and weakness.

Gabapentin (2 RCTs).

Both studies scored 4 out of 5 for validity.

Both studies reported benefits in terms of a reduction in spasticity on treatment with gabapentin versus placebo. The
lower-dose study reported ‘no serious side-effects’, while the other study did not report any adverse impact of gabapentin.

Threonine (1 RCT).

The study scored 5 out of 5 on the Jadad scale. Of the various outcomes used, only one showed a difference versus placebo (p=0.04) Further results relating to patient preferences, impact on function, and side-effects were reported in the review.

**Authors’ conclusions**

This review suggests that baclofen, dantrolene, diazepam and tizanidine are effective in reducing spasticity, as measured using the Ashworth scale or other clinical measures. There is, however, little evidence that these drugs lead to an improvement in patient function, and there is no evidence to suggest any difference between the drugs. The evidence that dantrolene has any effect on spasticity is of poor quality. Side-effects appear to be most common with diazepam and dantrolene, and least common with tizanidine. There are considerable limitations in the evidence available, and hence the conclusions that can be drawn from this review.

**CRD commentary**

The authors clearly stated their objective. However, a priori inclusion criteria relating to study design were not clear. While a number of databases were searched, only published English language articles were sought; it is therefore likely that relevant studies were missed. Differences between the studies were inspected and the studies were synthesised using a qualitative analysis. Some important details of the included studies were not reported. The outcome measures used and the results of each included study were not listed either in the text or in tables. When a particular result was reported for a study, it was sometimes unclear what outcome measure it related to. In addition, for some studies, only the total number of participants was reported, as opposed to the number of participants with MS. This lack of detail makes it difficult to determine the appropriateness of the included studies to the review question posed. The authors did not report any information relating to how decisions on the relevance of primary studies were made or how judgments of validity were made. Hence, it is not possible to assess how rigorous this process was. The authors state that the conclusions that can be drawn from these findings are limited, due to the limitations of the available evidence. The conclusions that have been drawn by the authors should be interpreted with caution in light of the highlighted caveats of the review.

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

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

**Research:** The authors state that there is a need for well-designed, large-scale studies that focus on patient functioning as an outcome. They state that such studies should clarify the extent of benefit which may be obtained both from the use of well-established treatments (in particular baclofen and tizanidine), as well as treatments not currently well established or licensed for this indication (such as gabapentin).

**Funding**

NHS Executive.

**Bibliographic details**


**PubMedID**

12166503
Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Humans; Multiple Sclerosis /complications; Muscle Relaxants, Central /administration & dosage; Muscle Spasticity /drug therapy /etiology

AccessionNumber
12002001657

Date bibliographic record published
31/08/2003

Date abstract record published
31/08/2003

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.