Cochrane Library

Cochrane Database of Systematic Reviews

Anti-spasticity agents for multiple sclerosis (Review)

Shakespeare D, Boggild M, Young CA

Shakespeare D, Boggild M, Young CA.
Anti-spasticity agents for multiple sclerosis.
Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD001332.
DOI: 10.1002/14651858.CD001332.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Anti-spasticity agents for multiple sclerosis

David Shakespeare[1], Mike Boggild[2], Carolyn A Young[2]

[1]Neuro-rehabilitation Unit, Lancashire Teaching Hospitals Trust, Preston, UK. [2]The Walton Centre for Neurology & Neurosurgery, Liverpool, UK

Contact address: David Shakespeare, Neuro-rehabilitation Unit, Lancashire Teaching Hospitals Trust, 32A Watling Street Rd, Preston, Lancashire, PR2 8DY, UK. david.shakespeare@lthtr.nhs.uk.

Editorial group: Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD001332. DOI: 10.1002/14651858.CD001332.

ABSTRACT

Background

Spasticity is a common problem in multiple sclerosis (MS) patients causing pain, spasms, loss of function and difficulties in nursing care. A variety of oral and parenteral medications are available.

Objectives

To assess the absolute and comparative efficacy and tolerability of anti-spasticity agents in MS patients.

Search methods

We searched the Cochrane MS Group trials register (June 2003), the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE (January 1966 to June 2003), EMBASE (January 1988 to June 2003), bibliographies of relevant articles, personal communication, manual searches of relevant journals and information from drug companies.

Selection criteria

Double-blind, randomised controlled trials (either placebo-controlled or comparative studies) of at least seven days duration.

Data collection and analysis

Two independent reviewers extracted data and the findings of the trials were summarised. Missing data were collected by correspondence with principal investigators. A meta-analysis was not performed due to the inadequacy of outcome measures and methodological problems with the studies reviewed.

Main results

Twenty-six placebo-controlled studies (using baclofen, dantrolene, tizanidine, botulinum toxin, vigabatrin, prazepam, threonine and cannabinoids) and thirteen comparative studies met the selection criteria and were included in this review. Only fifteen of these studies used the Ashworth scale, of which only three of the eight placebo-controlled trials and none of the seven comparative studies showed a statistically significant difference between test drugs. Spasms, other symptoms and overall impressions were only assessed using unvalidated scores and results of functional assessments were inconclusive.

Authors' conclusions

The absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. The rationale for treating features of the upper motor neurone syndrome must be better understood and sensitive, validated spasticity measures need to be developed.

PLAIN LANGUAGE SUMMARY

The effect of anti-spasticity agents in people with multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the nervous system which affects young and middle-aged adults. Spasticity, a common problem in people with MS, is a disorder of voluntary movement caused by damage to the central nervous system. The main sign is the resistance to passive movement of a limb but other associated features - pain, spasms, loss of function - affect people's quality of life more directly.

Many anti-spasticity drugs are available but the review of trials found that there is not enough evidence to compare their effectiveness. More research is needed.

BACKGROUND

Spasticity, defined as "a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome" (Lance 1980), is a significant problem for about 60% of MS patients (Smith 1991). It reduces mobility, makes transfers more difficult, is associated with painful muscular spasms and weakness, and predisposes to the development of contractures.

Drugs such as baclofen, diazepam, dantrolene and tizanidine are frequently used in an attempt to reduce spasticity and many others have been reported to have some anti-spasticity effect. All of these have different modes of action and different side-effect profiles which can limit their usefulness. It is thus important to document the efficacy and tolerability of these agents in order to guide rational prescribing and suggest directions for future research into the management of this often difficult problem.

The only widely used method available to assess the degree of spasticity is clinical assessment using the ordinal Ashworth Scale (Ashworth 1964; Wade 1992), which allocates a score between one and four depending on the difficulty in passively moving the limb of a relaxed patient. However this does not distinguish reflex- from non-reflex mediated causes of resistance to movement (Perry 1993) and it bears no clear relation to functional impairment (which can clearly be affected by many other factors) or occurrence of painful muscle spasms. In addition, function can be aided to a certain degree by spasticity (for example, walking can be possible despite leg weakness if spasticity maintains the anti-gravity posture). Thus assessing the effect of spasticity on a patient (and thus the role of anti-spasticity treatment) requires the use of several outcome measures.

OBJECTIVES

The objective of this review was to assess the absolute and comparative efficacy and tolerability of anti-spasticity agents in MS patients.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind, randomised controlled trials (RCTs) of treatment duration longer than seven days which are either placebo-controlled or comparing two or more agents were analysed. Quasi-randomised, unrandomised and unblinded trials were excluded. Cross-over trials were included and the authors were contacted to obtain information about the results of each period of the study.

Types of participants

Patients with a clinically definite diagnosis of MS (Poser 1983) at any stage of their disease and with spasticity of any degree were included. Patients within one month of a relapse were excluded. Studies including patients with other diagnoses were excluded unless individual data for the MS patients could be obtained either from the published results or through contact with the authors.

Types of interventions

Drug therapies reviewed were: baclofen (by oral or intra-thecal administration), diazepam, dantrolene, tizanidine, threonine, clonidine, 3,4-diaminopyridine, cyproheptadine, progabide, gabapentin, vigabatrin, oxcarbazepine, ketazolam, botulinum toxin and cannabinoids. Evidence for control for other factors which can affect spasticity (including use of other drugs (in particular benzodiazepines, anti-psychotic agents and anti-depressants), physiotherapy regimes, patients' mood, intercurrent and other illness) was sought.

Types of outcome measures

(1) Ashworth Scale (assessed double-blind)
(2) Functional assessment (using the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke 1983)
(3) Patient-reported functional status and muscle spasm frequency count
(4) Side-effect reports

Search methods for identification of studies

Electronic searches

(1) We searched the Cochrane Multiple Sclerosis Group trials register (June 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library, 2003, issue 2(Appendix 1), MEDLINE (PubMed) (from 1966 to June 2003) (Appendix 2), using the search strategy for randomised controlled trials of Dickersin and Larson (Clarke 1995), specifying the search for "spasticity" and "multiple sclerosis", and EMBASE (from 1988 to June 2003) (Appendix 3) using a similar strategy to that outlined for MEDLINE.

Searching other resources

(2) Searching reference lists from published reviews on symptom control in multiple sclerosis and identified RCTs.
(3) Personal communication with first authors of relevant trials or reviews, and other multiple sclerosis experts.
(4) Contacting drug manufacturers for baclofen (Novartis), dantrolene (Proctor and Gamble), tizanidine (Athena), gabapentin (Parke-Davis Medical), vigabatrin (Hoechst Marion Roussel), Botulinum toxin (Allergan & Ipsen) and any other drugs identified in relevant RCTs.
(5) Manual searches of the following journals: Multiple Sclerosis, Archives of Physical Medicine and Rehabilitation.

Unpublished trials were identified using strategies 3 and 4 above.

Data collection and analysis

Two independent reviewers screened titles and abstracts of papers identified using the above strategies to identify studies which met previously-defined inclusion criteria. Agreement was reached by consensus, after assessment of the full text of the paper and contacting the authors for further information where necessary. Two reviewers then independently abstracted the patient and study characteristics (including dose regimes, length of trial and outcome measures used) and the outcomes (as defined above). Final results were reached by consensus.

The methodological quality of the studies was assessed paying particular attention to: whether patients were truly randomised to the study groups; whether patients, the health care team and spasticity assessors were blind to assigned therapy; whether the

groups were truly identical in terms of stage of disease and pre-treatment spasticity level, progress of disease during the trial (e.g. number of relapses), other concomitant drug treatments, non-drug treatments for spasticity (e.g. physiotherapy regimes), assessment of spasticity and side-effects.

Analysis of outcomes was on an intention-to-treat basis. The first task of the review was to summarise evidence for the efficacy and tolerability of the different treatment regimens by documenting the change in Ashworth score, EDSS score, muscle spasm frequency count and side-effect reports in the study groups. Heterogeneity analyses were planned, comparing the log-odds-ratios for the Ashworth and EDSS scores calculated according to the proportional odds model (Whitehead 1994).

An attempt to carry out a meta-analysis of the Ashworth scale results was planned. As it is an ordinal scale, analysis of the individual patient data using a proportional odds model (Whitehead 1994) was thought to be more appropriate than simply treating it as if it were a continuous scale. Sensitivity analyses were planned to investigate the effect of methodological quality and severity of spasticity on the trial results. Results of the different periods of cross-over trials were included separately when available. Heterogeneity analyses were planned to investigate the effect of excluding all except the first treatment period of each cross-over study.

RESULTS

Description of studies

Thirty-nine of the 169 identified studies met the inclusion criteria (randomised, double-blind controlled trials of at least seven days duration).

(1) Oral baclofen versus placebo

Five crossover studies (Basmajian 1974; Basmajian 1975; Feldman 1978; Sawa 1979; Brar 1991) and one parallel-group study (Sachais 1977) have been reviewed. The results of the study reported in Basmajian 1975 included the participants previously reported in Basmajian 1974, as the two studies used identical methodology. Different daily doses of baclofen were used: three studies used 60 to 80 mg of baclofen, Brar 1991 used 20 mg, and Basmajian (Basmajian 1974; Basmajian 1975) titrated the dose according to effect (but the final dose used was not reported). Brar 1991 compared the effects of baclofen and placebo with and without a standardised programme of stretching exercises. Only Brar 1991 reported use of the Ashworth score.

(2) Dantrolene versus placebo

Three crossover trials (Gelenberg 1973; Sheplan 1975; Luisto 1982) and one parallel-group trial (Tolosa 1975) have been reviewed. No studies report using the Ashworth score.

(3) Tizanidine versus placebo

Three parallel-group trials have been reviewed (Lapierre 1987; Smith 1994; UKTTG 1994) using up to 36 mg tizanidine but only two reported use of the Ashworth scale (Smith 1994; UKTTG 1994). We have been unable to obtain further details of two unpublished studies described in Wallace 1994.

(4) Botulinum toxin versus placebo

Three studies evaluating the use of botulinum toxin (BT) have been identified (Snow 1990; Grazko 1995; Hyman 2000). Two (Snow 1990; Hyman 2000) evaluated participants with thigh adductor spasticity and one (Grazko 1995) evaluated four participants with lower limb spasticity and one participant with upper limb spasticity. Hyman 2000 reported a dose-ranging study, comparing 500, 1000 and 1500 units of Dysport with placebo.

(5) Vigabatrin versus placebo

Two unpublished cross-over trials have been identified (Tell 1981; Joder-Ohlenbusch '84) using 2 to 3 g daily of vigabatrin. Only Joder-Ohlenbusch '84 used the Ashworth scale.

(6) Cannabinoids versus placebo

Killestein 2002 reported a crossover study comparing the effects of delta9- tetrahydrocannabinol (THC), or C. sativa plant extract (containing a similar concentration of THC) with placebo. Wade 2003 reported a four-way crossover study comparing THC with cannabidiol (CBD), a 1:1 mixture of THC:CBD and placebo. Both studies reported assessment of the Ashworth scale.

(7) Other drugs assessed using placebo-controlled trials

One crossover study evaluating prazepam (Levine(1) 1969), three evaluating progabide (Mondrup 1984, Bovier 1985, Rudick 1987), one evaluating brolitene (Perkin 1976), and one evaluating L-threonine (Hauser 1992) have been identified. The trials of progabide and brolitene were omitted from the review as these drugs are not used therapeutically due to toxicity. Only Hauser 1992 reported use of the Ashworth scale.

(8) Comparison of baclofen and tizanidine

Six parallel-group studies (Chrzanowski 1981; Smolenski 1981; Wuthrich 1981; Stien 1987; Eyssette 1988; Pellkofer 1989) and one crossover study (Bass 1988), using baclofen doses up to 90 mg and tizanidine up to 36 mg, have been reviewed. Pellkofer 1989 also included a group treated with tetrazepam. Only Smolenski 1981; Stien 1987 and Pellkofer 1989 reported use of the Ashworth scale. Chrzanowski 1981 and Wuthrich 1981are reported in Wallace 1994 as using the Ashworth scale but only the change in level of spasticity is given in the unpublished research reports. It has not been possible to obtain further details of one unpublished study (Wickstrom 1987).

(9) Other comparative studies

From 1975 reported a crossover study comparing baclofen (30 to 120 mg; mean 61.2 mg) and diazepam (10 to 40 mg; mean 26.8 mg). Schmidt 1975 reported a four-way crossover study comparing high and low doses of diazepam (8 mg and 20 mg respectively) and dantrolene (100 mg and 300 mg respectively). Basmajian 1984 and Basmajian 1986 described two crossover studies comparing the two benzodiazepines, ketazolam and diazepam. Rinne 1980 described three comparative trials but only one restricted to MS patients - a parallel group study comparing tizanidine (maximum 18 mg) and diazepam (22.5 mg) in 30 patients. Jellinger 1983 reported a cross-over study comparing tizanidine with diazepam. Only From 1975 and Rinne 1980 reported use of the Ashworth score.

Risk of bias in included studies

(1) Oral baclofen versus placebo

Only Brar 1991 selected participants with clinically definite MS and no trials reported the method of randomisation used. Sawa 1979 also included participants with chronic myelopathy, presumed to

be MS. Most trials excluded patients with confounding conditions but Sachais 1977 included participants whose spasticity had varied in the month before the trial. All the crossover trials apart from Brar 1991 included a washout period between the arms of the trial but only Basmajian 1974; Feldman 1978 and Brar 1991 reported attempts to standardise the spasticity assessment. Only Brar 1991 used validated outcome measures (Ashworth score, Cybex isokinetic dynamometer (Bohannon 1987), and a questionnaire for subjective assessment of function adapted from the Minimal Record of Disability for MS (Haber 1985) but only results from the 30 patients who completed the study of the original 38 are reported and in summary form only. Feldman 1978 used an unvalidated spasm score and a resistance to passive movement score which is similar but not identical to the Ashworth score and the results are only tabulated for those who showed an improved score; results were only reported for the 23 out of 33 patients who completed the trial.

(2) Dantrolene versus placebo

No trials report the diagnostic criteria or the method of randomisation used. Only Sheplan 1975 reports attempts to standardise assessment conditions but no validated outcome measures were used in any of the trials. Luisto 1982 included three MS participants and provided some individual patient data on request; blinding was compromised by a change in urine colour with dantrolene.

(3) Tizanidine versus placebo

Only UKTTG 1994 reported the diagnostic criteria used and none of the three trials described the method of randomisation. All trials excluded participants with confounding conditions and other medication which could affect muscle tone was withdrawn before the trials commenced. In UKTTG 1994, blinding could have been compromised by using the same doctor as assessor and prescriber during the titration phase in some centres. Smith 1994 made some attempt to standardise assessment conditions. In both Smith 1994 and UKTTG 1994 significant numbers did not complete the full protocol (Smith 1994: 37 participants were excluded from the analysis and 76/111 in the tizanidine group and 83/109 in the placebo group completed the study; UKTTG 1994: 155 of the 187 recruited participants completed the study with little protocol violation (medication compliance > 75 % and attendance at five of eight assessments - 75/94 tizanidine and 80/93 placebo) but only 70 (29 tizanidine, 41 placebo) complied with the study protocol completely).

In UKTTG 1994, a composite "Ashworth" score was calculated combining results from assessments of ten muscle groups on each side (i.e. maximum possible score for a quadriplegic participant was 80, for a hemiplegic participant was 40 and a paraplegic participant was 32: patterns of spasticity in the two groups are not reported although the overall level of spasticity was said to be similar in each group). The group mean composite Ashworth score was calculated for each group at each visit and compared to that at baseline. Multiple statistical analyses were carried out on the many outcome measures but not corrected for multiple comparisons. Smith 1994 reports fewer details of the assessment of the Ashworth score but a similar method seems to have been used. Lapierre 1987 did not use the Ashworth scale.

(4) Botulinum toxin (BT) versus placebo

In Grazko 1995, the method of randomisation is not described and the dose of BT was determined according to muscle size. The method of assessment of spasm scores is not described.

Hyman 2000 did not report the method of randomisation used. Participants with fixed hips due to established contractures, those who had suffered recent relapse and those who had recent focal or intrathecal anti-spasticity medication were excluded. The groups were well-matched for age, weight, duration of MS, degree of spasticity and EDSS score, but fewer participants in the placebo group were receiving concomitant anti-spasticity agents or analgesics. Participants continued regular physiotherapy and other concomitant anti-spasticity medication at a constant level throughout the study. A total spasticity score (product of a modified Ashworth scale and spasm frequency) was reported, which was partially validated in Snow 1990 below.

Snow 1990 used a table of random numbers to assign the order of treatments and used rating scales which had only been partially validated (for inter-rater reliability, but not for intra-rater reliability or variability over time). The muscle tone scale used was based on but not identical with the Ashworth scale. The participants had stable spasticity and were taking no other anti-spasticity medication. Results are presented showing the change in rating scales from the onset of that arm of the trial but the absolute starting point for each arm of the trial is not reported. One of the placebo-treated participants was withdrawn from the trial after the first injection due to the development of a left hemi-paresis.

(5) Vigabatrin versus placebo

Neither study reported the diagnostic criteria or the method of randomisation used. Only Joder-Ohlenbusch '84 reported avoidance of confounding factors (other anti-spasticity medication or physiotherapy) and neither trial reported attempts to standardise assessment conditions. Both trials used unvalidated spasms scores and only Joder-Ohlenbusch '84 reported use of the Ashworth scale.

(6) Cannabinoids versus placebo

Killestein 2002 excluded participants who had had a recent relapse, steroid or cannabinoid exposure, but did not report use of other anti-spasticity medication or physiotherapy treatment. The method of randomisation used was not reported, and blinding was probably compromised as patients (but not the assessing physicians) often guessed correctly which treatment they were taking. Outcome measures used included the mean Ashworth score, EDSS and visual analogue scores.

Wade 2003 included participants with intractable neurogenic symptoms (including spasticity) unresponsive to standard medications whose symptoms were stable, but no fixed criteria of baseline stability were reported. Blinding is likely to have been compromised as participants were required to use open label cannabinoid prior to commencing the study for safety reasons. Use of rescue medications was reported but concomitant physiotherapy treatment was not. Participants were permitted to titrate to the most effective dose during the first of each two week period, but there was no washout period between the treatment periods. Outcome measures used included the mean Ashworth score, mean self-rated visual analogue scales (collected over days 8 to 14 of each two week period) and two-weekly investigator numerical assessment of symptoms.

(7) Other drugs assessed using placebo-controlled trials
Hauser 1992 selected participants with clinically definite MS who had been stable for at least one year. Participants were excluded if they had joint disease which would hinder assessment, required psychotropic drugs, or had received anti-spasticity treatment in the previous one month or chemotherapeutic agents in the previous six months. Randomisation was controlled by pharmacy. The movements used to assess Ashworth score were not described and results only reported as the group mean and Standard Error of the Mean (SEM). Results for other parameters were only reported qualitatively. This trial will not be assessed further.

(8) Comparison of baclofen and tizanidine
Only Bass 1988 reported the diagnostic criteria used and only Pellkofer 1989 reported the method of randomisation used (minimisation). Smolenski 1981 allowed participants to continue taking regular hypnotic or psychotropic medication during the trial but other trials withdrew confounding medication. Attempts to standardise the assessment conditions were only reported in Bass 1988. Chrzanowski 1981 and Wuthrich 1981 will not be described further as details of the methods of assessment of spasticity, spasms, clonus and function were not given, and the final drug doses used were not reported in Chrzanowski 1981. Only unvalidated measures of muscle strength were reported in the included trials.

(9) Other comparisons
No trials reported the diagnostic criteria or the method of randomisation. Only the ketazolam/diazepam comparative studies of Basmajian 1984 and Basmajian 1986 reported attempts to standardise examination conditions.

Effects of interventions

A meta-analysis was not attempted in view of concerns about the validity of the Ashworth scale (Pandyan 1999), differences in the way the Ashworth score was assessed and inability to obtain results for the different treatment periods of crossover studies. No trials reported use of a validated spasm score. A summary of the findings of the trials is presented below.

(1) Oral baclofen versus placebo
Brar 1991 reported significant improvement compared to placebo in angle of flexion and subjective function report for participants treated with baclofen alone or in combination with stretching exercises, but no significant added benefit from stretching exercises alone. Significantly more participants improved in Ashworth score only with baclofen combined with exercises compared with placebo.

Feldman 1978 only reported the numbers of participants who improved on each treatment. Significantly better improvement was suggested in passive range of motion, painful spasms and clonus in participants taking baclofen.

(2) Dantrolene versus placebo
No conclusions on efficacy can be drawn as no validated outcome measures were used.

(3) Tizanidine versus placebo
Smith 1994 reported Ashworth scores as changes from baseline in total score for all four limbs and lower limbs only (as few participants noted upper limb spasticity) and the percentage of participants showing an improvement in total Ashworth score; no significant difference was noted for the tizanidine- or placebo-treated groups in either parameter and a large placebo response was noted. Changes from baseline in total spasm and clonus scores were found not to be normally distributed, and a significantly greater effect for tizanidine was only noted after transformation of raw scores to response ratios and the performance of non-parametric statistics on the median values (post hoc analysis). No significant differences between the groups were noted in secondary end-points (including muscle power), except a better global efficacy and tolerability score (using a 11.5 cm analogue scale) with tizanidine. Large numbers of adverse events were reported (61% of placebo-treated group, 91% of tizanidine-treated group). Fourteen participants discontinued tizanidine because of side-effects (cf. six placebo): four due to dry mouth (two in placebo group), four due to somnolence, three due to dizziness (one in placebo group) and one due to drug-induced hepatitis and hallucinations.

In UKTTG 1994, no relationship was found between the initial total muscle-tone score and dose of medication found to be optimal in the titration phase. Mean daily dose of drugs used at the end of the three-week titration phase (tizanidine 30.7 mg, placebo 35.0 mg) fell during the nine-week maintenance phase to 25.2 mg for tizanidine and 33.6 mg placebo at the end of the study. Ashworth score results were reported for all 187 randomised participants as change from baseline in group mean total Ashworth scores for all 10 muscle groups in all limbs (tizanidine 18.5 (SD 9.4) at baseline to 14.6 (SD 10.1) versus placebo 16.8 (SD 11.1) to 15.3 (SD 10.0), which was reported as being statistically significant ($p = 0.004$) using analysis of variance) and as percentage of participants noting an improvement of one point or more (71% with tizanidine and 50% with placebo, reported as being statistically significant ($p < 0.005$)). The clinical significance of this finding cannot be evaluated as many muscle groups were assessed. No significant difference was noted between the tizanidine- and placebo-treated groups in EDSS, Medical Reasearch Council power grade, spasm score, pain score or eight metre walk time. Results for other secondary analyses were reported as an overall impression of change. Twenty-nine participants discontinued tizanidine prematurely (12 due to adverse effects of tiredness, drowsiness or dry mouth; 12 due to inefficacy, three due to poor co-operation, one because of an unrelated illness and one because of withdrawal effects from previous anti-spasticity medication).

There were no statistically significant differences between tizanidine and placebo in any of the validated assessment methods reported by Lapierre 1987.

(4) Botulinum toxin (BT) versus placebo
In Grazko 1995 , all five participants showed a two point improvement in Ashworth score which persisted for one to three months, and a similar improvement in spasm scores was reported (results not shown) after injection of the active agent. There was no placebo effect.

In Hyman 2000, there was a statistically significant improvement greater than placebo only in the maximum distance between the knees in the 1500 unit group at the primary end-point of four weeks, but no statistically significant difference in the Ashworth scale scores. Time to requiring re-treatment was significantly greater in all BT groups than placebo. Improvement in total spasticity score was similar in all groups compared to baseline. There were more frequent reports of weakness with the botulinum toxin groups

(especially at the 1500 unit dose), but otherwise reports of side-effects were similar. Some difference between the groups may have been masked by the more frequent use of concomitant anti-spasticity medication in the BT-treated groups.

In Snow 1990, 7/9 participants treated with BT showed an improvement in spasticity score (product of tone and spasm scores) compared with 1/9 on placebo. One participant on BT and two on placebo showed a deterioration in this score. Seven of nine participants showed an improvement in hygiene scores on BT, compared to two on placebo.

(5) Vigabatrin versus placebo

Joder-Ohlenbusch '84 reported improvement in Ashworth score in the same number of participants with vigabatrin and placebo, but more participants with vigabatrin improved in unvalidated spasm score. Tell 1981 noted no significant difference between vigabatrin and placebo in unvalidated spasticity and spasm scores.

(6) Cannabinoids versus placebo

Killestein 2002 and Wade 2003 both reported no significant difference in mean Ashworth score in either of the two active treatment groups compared to placebo. Killestein 2002 noted a worsening in the brainstem functional systems score in the plant extract group, and a worsening in the total MS functional composite score (9 hole peg test, 25 feet timed walk, Paced Auditory Serial Addition Test) and participant' subjective global rating in the delta9- tetrahydrocannabinol (THC) treated group. Wade 2003 reported a significant improvement in mean VAS scores for pain, spasms and spasticity, and numerical rating of spasticity severity and spasm frequency compared to placebo.

(8) Comparison of baclofen and tizanidine

Bass 1988 reported results only for the 48/66 participants who completed both treatment arms; four were excluded due to protocol violation, two due to relapse, 11 due to weakness (baclofen seven, tizanidine four), and five (on baclofen) due to nausea. Mean daily doses at the end of the treatment periods were 17.4 mg for tizanidine (range 2 to 36 mg) and 34.9 mg for baclofen (range 5 to 80 mg). No significant difference was noted in the EDSS or the unvalidated tone measures for either drug. Participants, physicians and physiotherapists generally found baclofen to be more effective than tizanidine.

Smolenski 1981, Stien 1987, Eyssette 1988 and Pellkofer 1989 detected no significant differences at the doses of baclofen and tizanidine used in effects on spasticity, spasms or clonus. Only Smolenski 1981 and Stien 1987 noted changes in objective muscle power (although by unvalidated or undescribed scales) with slightly more participants noting a deterioration with baclofen than tizanidine. All trials noted that slightly more participants reported weakness with baclofen than tizanidine.

(9) Other comparisons

From 1975 did not detect a significant difference between baclofen and diazepam in any of the outcome measures, except more sedation on diazepam (eleven versus five participants) and global physician preference more often for baclofen (twelve versus four comparisons). Similarly, Schmidt 1975 (detected no difference between dantrolene and diazepam, except more sedation on diazepam (28 versus 13 participants) and overall participant preference was more often for dantrolene (22 versus 13 participants). The ketazolam/diazepam comparison of Basmajian 1984 and Basmajian 1986 showed no significant preference for either drug. The tizanidine/diazepam comparison of Rinne 1980 showed no significant difference in the efficacy of the two drugs but more weakness and drowsiness with diazepam; tizanidine was generally preferred. Jellinger 1983 noted improvement in muscle tone, spasms and clonus more frequently in those taking tizanidine (assessment methods not described) and fewer participants reported tiredness or dizziness than with diazepam.

DISCUSSION

Evaluating the absolute and comparative efficacy of drug treatments for a clinical problem requires an understanding of the phenomenology of the problem and the ability to measure it. When considering the problem of spasticity it is clear that both our understanding of the problem (its pathophysiology, clinical manifestations and effect on the daily life of patients) and our ability to measure it are seriously deficient. This is reflected in the wide variety of approaches taken to assess spasticity in the trials we have reviewed and the inconclusive objective results of the vast majority of the trials.

Methodological quality of trials (especially in the control for confounding factors and the choice of assessment tools which are validated for inter- and intra-rater reliability) is clearly improving, if one compares the baclofen trials of the 1970s with the tizanidine trials of the 1990s. However, difficulty remains in even demonstrating the efficacy of active drug against placebo (quite apart from the statistical difficulty in assessing non-parametric scales and the complexity of multiple sclerosis compared with monophasic conditions such as stroke and spinal cord injury). There remains a gap between published evidence and the daily experience of those who manage spasticity. Better assessment tools are needed to confirm the clinical impression that the widely used anti-spasticity drugs (baclofen, dantrolene, tizanidine) are more effective that placebo. Only then can comparative studies be expected to evaluate the comparative efficacy of different agents.

The validity of the Ashworth scale, the only widely used assessment tool for spasticity, has been seriously questioned (Pandyan 1999) and we are not aware of any validated method of assessing spasm scores. Sixteen of the studies we have summarised reported an "Ashworth scale" (From 1975; Rinne 1980; Chrzanowski 1981; Smolenski 1981; Wuthrich 1981; Joder-Ohlenbusch '84;Stien 1987; Brar 1991; Hauser 1992; Smith 1994; UKTTG 1994; Grazko 1995; Pellkofer 1989; Hyman 2000; Killestein 2002; Wade 2003) but used different methods to assess and score the Ashworth scale results, so a meta-analysis was not attempted. Only three (Brar 1991; UKTTG 1994; Grazko 1995) of the placebo-controlled (absolute efficacy) trials which reported Ashworth scale results showed a statistically significant superior effect of active drug over placebo. None of the comparative studies were able to show a statistical difference between the trial drugs.

The concept of weakness reported by patients with spasticity is poorly characterised. A patient reporting weakness may be referring to a reduction in static limb muscle power (although scant evidence for this was present in these trials), reduction in power of postural trunk muscles, fatigue or some other central effect. Evidence for differences between drugs was limited to unvalidated limb power scores and patient side-effect reports (cf. baclofen/tizanidine comparative trials). Also, the finding that "more patients report weakness with drug A than drug B" does not necessarily

imply that patients on drug A will notice an increase in muscle power if they are changed to drug B.

The decision to treat a patient with anti-spasticity medication is made for different reasons in different patients, especially in a disease with such varied clinical manifestations as multiple sclerosis: the immobile patient is treated for symptomatic relief (pain and spasms) and in order to make nursing care and seating easier, whereas the ambulant patient is treated with the additional aim of improving or preserving mobility. Different manifestations of the upper motor neurone syndrome are treated in different cases (e.g spasms, associated reactions) and it cannot be assumed that the effect on resistance to passive stretch can be taken as a surrogate marker for all these: the diagnostic examination of the neurologist is not always an adequate predictor of the functional examination of the physiotherapist or the daily experience of the patient. The currently available evidence does not help to answer the question of which agents are best for treating different spasticity scenarios. The development of more appropriate outcome measures will require better phenomenological and neurophysiological characterisation of these spasticity scenarios, probably by a multidisciplinary neuro-rehabilitation team.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review has identified a large number of studies which have attempted to assess the absolute and comparative efficacy of various anti-spasticity agents in multiple sclerosis. The variability of spasticity and the lack of a sensitive, reliable, functionally- and symptomatically-relevant assessment tool for spasticity have contributed to the inconclusive results of placebo-controlled trials attempting to document the efficacy of anti-spasticity agents which are in widespread use. Comparative studies have been similarly inconclusive. No firm recommendations to change practice can be made from this systematic review, and in particular there is no good evidence to prefer newer over older agents.

Implications for research

There is an urgent need for assessment tools for spasticity and other components of the upper motor neurone syndrome which are sensitive and well-validated. Such measures must correspond to the daily patient experience of spasticity and be used in comparative studies of older and newer drugs before firm recommendations to change to newer agents can be made. Studies of anti-spasticity medication should not be carried out without similar studies of the non-drug management of spasticity. The recognition that there are a variety of spasticity scenarios and reasons for wanting to treat spasticity may assist the design of trials which are likely to be able to answer the questions posed by the day-to-day management of multiple sclerosis patients troubled by spasticity.

ACKNOWLEDGEMENTS

We received invaluable help in obtaining references from the Librarians at the Postgraduate Library, University Hospital Aintree, the Librarians at the British Medical Association Library, London, and from Dr Lee Durham (Macon, Georgia, USA). Patrick Weiderseiner and Dr Ian Scott provided translations of some of the foreign language articles.

We thank the following experts for commenting on our protocol and assisting us in identifying relevant trials: Prof R Hohlfield & Dr F Then Bergh (Munich, Germany), Dr M Kita & Dr D E Goodkin (San Francisco, USA), Prof D Wade (Oxford, UK), Prof M Barnes (Newcastle, UK), Prof O Hommes (Nijmegen, Netherlands), Prof A Thompson (London, UK), Prof B Arnason (Chicago, USA), Dr R T Schapiro (Minneapolis, USA).

We thank the following pharmaceutical companies for assisting us in the identification of published and unpublished trials, for providing copies of some references and for providing details of unpublished trials as noted in the review: Novartis, Proctor and Gamble, Athena, Elan Pharma, Parke-Davis Medical, Aventis Pharma, Allergan, Ipsen.

REFERENCES

References to studies included in this review

Basmajian 1974 *{published data only}*

* Basmajian JV, Yucel V. Effects of GABA-derivative (BA-34647) on spasticity. Preliminary report of a double-blind cross-over study & rehabilitation. *American Journal of Physical Medicine* 1974;**53**(5):223-8.

Basmajian 1975 *{published data only}*

* Basmajian JV. Lioresal (baclofen) treatment of spasticity in multiple sclerosis. *American Journal of Physical Medicine* 1975;**54**(4):175-7.

Basmajian 1984 *{published data only}*

* Basmajian JV, Shankardass K, Russell D. Ketazolam treatment for spasticity: double-blind study of a new drug. *Archives of Physical Medicine & Rehabilitation* 1984;**65**(11):698-701.

Basmajian 1986 *{published data only}*

* Basmajian JV, Shankardass K, Russell D. Ketazolam once daily for spasticity: double-blind cross-over study. *Archives of Physical Medicine and Rehabilitation* 1986;**67**(8):556-7.

Bass 1988 *{published data only}*

* Bass B, Weinshenker B, Rice GP, Neseworthy JH, Cameron MG, Hader W, et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. *Canadian Journal of Neurological Sciences* 1988;**15**(1):15-9.

Bovier 1985 *{published data only}*

* Bovier P, Cambier J, Morselli PL. Double-blind study of progabide in spasticity [Etude en double-aveugle du progabide dans le spasticite]. *Therapie* 1985;**40**(3):181-5.

Brar 1991 *{published data only}*

* Brar Sp, Smith MB, Nelson LM, Franklin GM, Cobble ND. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. *Archives of Physical Medicine & Rehabilitation* 1991;**72**(3):186-9.

Chrzanowski 1981 *{unpublished data only}*

Chrzanowski K. A comparative trial of tizanidine and baclofen in the treatment of spasticity due to multiple sclerosis (study no. 26). Unpublished Sandoz Research Report 1981.

* Chrzanowski, C. A new muscle relaxant, DS 103-282, versus baclofen in the treatment of chronic spasticity. 8th International Congress of Physical Medicine & Rehabilitation. Sweden: Print Minab, 1980:45.

Eyssette 1988 *{published data only}*

* Eyssette M, Rohmer F, Serratrice G, Warter JM, Boisson D. Multi-centre, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. *Current Medical Research & Opinion* 1988;**10**(10):699-708.

Feldman 1978 *{published data only}*

* Feldman RG, Kelly-Hayes M, Conomy JP, Foley JM. Baclofen for spasticity in multiple sclerosis. Double-blind crossover and three-year study. *Neurology* 1978;**28**(11):1094-8.

From 1975 *{published data only}*

* From A, Heltberg A. A double-blind trial with baclofen (Lioresal) and diazepam in spasticity due to multiple sclerosis. *Acta Neurologica Scandinavica* 1975;**51**(2):158-66.

Gelenberg 1973 *{published data only}*

* Gelenberg AJ, Poskanzer DC. The effect of dantrolene sodium on spasticity in multiple sclerosis. *Neurology* 1973;**23**(12):1313-5.

Grazko 1995 *{published data only}*

* Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. *Neurology* 1995;**45**(4):712-7.

Hauser 1992 *{published data only}*

* Hauser SL, Doolittle TH, Lopez-Bresnahan M, Shahani B, Schoenfeld D, Shin VE, et al. An antispasticity effect of threonine in multiple sclerosis. *Archives of Neurology* 1992;**49**(9):923-6.

Hyman 2000 *{published data only}*

* Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreeczy-Kleedorfer B, et al. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. *Journal of Neurology, Neurosurgery & Psychiatry* 2000;**68**(6):707-12.

Jellinger 1983 *{unpublished data only}*

Jellinger K. [Zur Behandlung der Spastizitat bei multipler Sklerose-Ergebnisse einer Doppelblindstudies mit Tizanidin und Diazepam]. In: Conrad B, Benecke R, Bauer H editor(s). Die klinische Wertung der Spastizitat. Stuttgart: Schattauer, 1984:171-185.

* Jellinger K. A controlled, double-blind, clinical, therapeutic, comparative study with two parallel groups (tizanidine and diazepam) in ambulant/hospitalized patients with multiple sclerosis. Unpublished Sandoz Research Report 1983.

Joder-Ohlenbusch '84 *{unpublished data only}*

* Joder-Ohlenbusch AM, Schechter PJ. Double-blind, placebo-controlled, crossover study of -vinyl GABA treatment in spasticity. Unpublished Research Report 1984.

Killestein 2002 *{published data only}*

* Killestein J, Hoogervorst ELJ, Reif M, Kalkers NF, van Loenen AC, Staats PGM, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002;**58**(9):1404-7.

Lapierre 1987 *{published data only}*

* Lapierre YD, Bouchard S, Tansey C, Gedron D, Barkas WJ, Francis CB. Treatment of spasticity with tizanidine in multiple

sclerosis. *Canadian Journal of Neurological Sciences* 1987;**14**(3 Suppl):513-7.

Levine(1) 1969 *{published data only}*

* Levine I, Jossmann PB, Friend DG, DeAngelis V. Prazepam in the treatment of spasticity. A quantitative double-blind evaluation. *Neurology* 1969;**19**(5):510-6.

Luisto 1982 *{published and unpublished data}*

* Luisto M, Moller K, Nuutila A, Palo J. Dantrolene sodium in chronic spasticity of varying etiology. A double-blind study. *Acta Neurologica Scandinavica* 1982;**65**(4):355-62.

Pellkofer 1989 *{published and unpublished data}*

* Pellkofer M, Paulig M. Comparative double-blind study of the effectiveness and tolerance of baclofen, tetrazepam and tizanidine in spastic movement disorders of the lower extremities. *Medizinische Klinik* 1989;**84**(1):5-8.

Rinne 1980 *{published data only}*

* Rinne U. Tizanidine treatment of spasticity in multiple sclerosis and chronic myelopathy. *Current Therapeutic Research* 1980;**28**:827-36.

Sachais 1977 *{published data only}*

* Sachais BA, Logue JN, Carey MS. Baclofen, a new antispastic drug. A controlled, multicenter trial in patients with multiple sclerosis. *Archives of Neurology* 1977;**34**(7):422-8.

Sawa 1979 *{published data only}*

* Sawa GM, Paty DW. The use of baclofen in treatment of spasticity in multiple sclerosis. *Canadian Journal of Neurological Sciences* 1979;**6**(3):351-4.

Schmidt 1975 *{published data only}*

Schmidt RT Lee RH, Spehlmann R. Treatment of spasticity in multiple sclerosis: comparison of dantrolene sodium and diazepam. *Transactions of the American Neurology Association* 1975;**100**:235-7.

* Schmidt RT, Lee RH, Spehlmann R. Comparison of dantrolene sodium and diazepam in the treatment of spasticity. *Journal of Neurology, Neurosurgery & Psychiatry* 1976;**39**(4):350-6.

Sheplan 1975 *{published data only}*

* Sheplan L, Ishmael C. Spasmolytic properties of dantrolene sodium: Clinical evaluation. *Military Medicine* 1975;**140**(1):26-9.

Smith 1994 *{published data only}*

* Smith C, Birnbaum G, Carter Jl, Greenstein J, Lublin FD. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. *Neurology* 1994;**44 Suppl 9**(11):S34-42.

Smolenski 1981 *{published data only}*

* Smolenski C, Muff S, Smolenski-Kautz S. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. *Current Medical Research & Opinion* 1981;**7**(6):374-83.

Snow 1990 *{published data only}*

* Snow BJ, Tsui JK, Bhatt MH, Varelas M, Hashimoto SA, Calne DB-. Treatment of spasticity with botulinum toxin: a double-blind study. *Annals of Neurology* 1990;**28**(4):512-5.

Stien 1987 *{published data only}*

* Stien R, Nordal HJ, Oftedal SI, Slettebo M. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. *Acta Neurologica Scandinavica* 1987;**75**(3):190-4.

Tell 1981 *{unpublished data only}*

* Tell G. Double-blind, placebo-controlled crossover study of multiple oral doses of RMI 71,754 (Vigabatrin) in ten hospitalised patients with muscle spasticity. Unpublished Research Report 1981.

Tolosa 1975 *{published data only}*

* Tolosa ES, Soll RW, Loewenson RB. Treatment of spasticity in multiple sclerosis with dantrolene. *Journal of American Medical Association* 1975;**233**(10):1046.

UKTTG 1994 *{published data only}*

* The United Kingdom Tizanidine Trial Group. A double-blind placebo-controlled trial of tizanidine in the treatment of spasticity caused by multiple sclerosis. *Neurology* 1994;**44 Suppl 9**(11):S70-S78.

Wade 2003 *{published data only}*

* Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clinical Rehabilitation* 2003;**17**(1):21-9.

Wuthrich 1981 *{unpublished data only}*

* Wuthrich, R. A comparative trial of tizanidine and baclofen in the treatment of spasticity due to multiple sclerosis (study No 31). Unpublished Sandoz Research Report 1981.

References to studies excluded from this review

Abel 1994 *{published data only}*

* Abel NA, Smith RA. Intrathecal baclofen for treatment of intractable spinal spasticity. *Archives of Physical Medicine & Rehabilitation* 1994;**75**(1):54-8.

Anonymous 1973 *{published data only}*

* Anonymous. A phenothiazine in spasticity. *Practitioner* 1973;**210**(257):429-31.

Anonymous 1974 *{published data only}*

* Anonymous. A comparative trial of dimethothiazine in spastic conditions. *Practitioner* 1974;**213**(1273):101-5.

Azouvi 1996 *{published data only}*

* Azouvi P, Mane M, Thiebaut JB, Denys P, Remy-Neris O, Bussel B. Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. *Archives of Physical Medicine & Rehabilitation* 1996;**71**(1):35-9.

Barat 1974 *{published data only}*

* Barat M, et al. Treatment of spasticity with Lioresal: clinical trial involving 47 cases. *Bordeaux Medical* 1974;**7**:1435-8.

Barbeau 1982 *{published data only}*

* Barbeau H, Richards CL, Bedard PJ. Action of cyproheptadine in spastic paraparetic patients. *Journal of Neurology, Neurosurgery & Psychiatry* 1982;**45**(10):923-6.

Basmajian 1973 *{published data only}*

* Basmajian JV, Super GA. Dantrolene sodium in the treatment of spasticity. *Archives of Physical Medicine & Rehabilitation* 1973;**54**(2):61-4.

Baykuschev 1968 *{published data only}*

* Baykuschev S. [The effect of chlorpromazine on inhibitory processes in the spinal cord of patients with spastic paralyses] [German]. *Deutsche Zeitschrift fur Nervenheilkunde* 1968;**194**(4):318-27.

Becker 1995 *{published data only}*

* Becker WJ, Harris CJ, Long ML, Ablett DP, Klein GM, De Forge DA. Long-term intrathecal baclofen therapy in patients with intractable spasticity. *Canadian Journal of Neurological Sciences* 1995;**22**(3):208-17.

Behan 1982 *{published data only}*

* Behan P. An evaluation of low dose dantrolene sodium (Dantrium) therapy in the treatment of ambulatory patients with spasticity. *Clinical Trials Journal* 1982;**19**:1-8.

Bergamini 1966 *{published data only}*

* Bergamini L, Riccio A, Bergamasco B. A drug with antispastic action on striated muscle. Clinical Trial of derivative of GAVA [Un farmaco ad azione antispastica della musculatura striata. Sperimentazione clinica di un derivativo del GABA]. *Minerva Medica* 1966;**57**(65):2723-29.

Bianchi 1999 *{published data only}*

* Bianchi L, Monaldi F, Paolucci S, Iani C, Lacquaniti F. Quantitative analysis of the pendulum test: application to multiple sclerosis patients treated with botulinum toxin. *Functional Neurology* 1999;**14**(2):79-92.

Birkmayer 1967 *{published data only}*

* Birkmayer W, Danielczynk W, Weiler G. [An objective assessment of the monolytic effects of an aminobuutyric acid derivative (CIBA 34647-Ba)] [German]. *Wiener Medizinische Wochenschrift* 1967;**117**(1):7-9.

Bittencourt 1988 *{published data only}*

* Bittencourt PR. Oxcarbazepine and spasticity: further observations. *Arquivos de Neuro-Psiquiatria* 1988;**46**(4):382-4.

Broggi 1993 *{published data only}*

* Broggi G, Servello D, Brocks S, Dones I. The treatment of spasticity by intrathecal administration of baclofen: a preliminary personal experience. *Journal of Neurosurgical Sciences* 1993;**37**(4):203-8.

Broseta 1989 *{published data only}*

* Broseta J, Morales F, Garcia-March G, Sanchez-Ledesma MJ, Anaya J, Gonzales-Darder J, et al. Use of intrathecal baclofen administered by programmable infusion pumps in resistant spasticity. *Acta Neurochirurgica* 1989;**46 Suppl**:39-45.

Burke 1971 *{published data only}*

* Burke D, Andrews CJ, Knowles L. The action of a GABA derivative in human spasticity. *Journal of the Neurological Sciences* 1971;**14**(2):199-208.

Cartlidge 1974 *{published data only}*

* Cartlidge NE, Hudgson P, Weightman D. A comparison of baclofen and diazepam in the treatment of spasticity. *Journal of the Neurological Sciences* 1974;**23**(1):17-24.

Castaigne 1973 *{published data only}*

* Castaigne JP, Laplane D, Pierrot-Deseilligny E, Bussel B, Macquart-Moulin J. [Trial of Lioresal in the treatment of spasticity] [French]. *Nouvelle Presse Medicale* 1973;**2**(35):2341-2.

Cendrowski(1) 1977 *{published data only}*

* Cendrowski W, Sobczyk W. Clonazepam, baclofen and placebo in the treatment of spasticity. *European Neurology* 1977;**16**(1-6):257-62.

Cendrowski(2) 1977 *{published data only}*

* Cendrowski W. Dantrium in the treatment of increased muscle tonus in patients with multiple sclerosis. *Neurologia I Neurochirurgia Polska* 1977;**11**(1):117-21.

Chantraine 1980 *{published data only}*

* Chantraine A, van Ouwenaller C. [Treatment of spasticity in neurological disease by dantrolen-sodium] [German]. *Nervenarzt* 1980;**51**(1):50-4.

Chipman 1974 *{published data only}*

* Chipman M, Kaul S, Lambie M. Efficacy of dantrolene sodium in the treatment of spasticity. *Diseases of the Nervous System* 1974;**35**:427ff.

Chyatte 1971 *{published data only}*

Chayatte SB, Birdsong JH. The use of dantrolene sodium in disorders of the central nervous system. *Southern Medical Journal* 1971;**64**(7):830-4.

Coffey 1993 *{published data only}*

* Coffey RJ, Cahill D, Steers W, Park TS, Ordia J, Meythaler J, et al. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. *Journal of Neurosurgery* 1993;**78**(2):226-32.

Cohan 1980 *{published data only}*

* Cohan SL, Raines A, Panagakos J, Armitage P. Phenytoin and chlorpromazine in the treatment of spasticity. *Archives of Neurology* 1980;**37**(6):360-4.

Corston 1981 *{published data only}*

* Corston RN, Johnson F, Godwin-Austen RB. The assessment of drug treatment of spastic gait. *Journal of Neurology, Neurosurgery & Psychiatry* 1981;**44**(11):1035-9.

Cumming 1972 *{published data only}*

* Cumming R. Multiple sclerosis in the Shetlands, with an evaluation of Lioresal. *Postgraduate Medical Journal* 1972;**48**(Suppl 5):34-6.

Cutter 2000 *{published data only}*

* Cutter NC, Scott DD, Johnson JC, Whiteneck G. Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. *Archives of Physical Medicine and Rehabilitation* 2000;**81**(2):164-9.

Dressnandt 1996 *{published data only}*

* Dressnandt J, Conrad B. Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *Journal of Neurology, Neurosurgery & Psychiatry* 1996;**60**(2):168-73.

Duncan 1976 *{published data only}*

* Duncan GW, Shahani BT, Young RR. An evaluation of baclofen treatment for certain symptoms in patients with spinal cord lesions. A double-blind, cross-over study. *Neurology* 1976;**26**(5):441-6.

Dunevsky 1998 *{published data only}*

* Dunevsky A, Perel AB. Gabapentin for relief of spasticity associated with multiple sclerosis. *American Journal of Physical Medicine & Rehabilitation* 1998;**77**(5):451-4.

Emre 1994 *{published data only}*

* Emre M, Leslie GC, Muir C, Part NJ, Pokorney R, Roberts RC. Correlations between dose, plasma concentrations and antispastic action of tizanidine (Sirdalud). *Journal of Neurology, Neurosurgery & Psychiatry* 1994;**57**(11):1355-9.

Finnimore 1995 *{published data only}*

* Finnimore AJ, Roebuck M, Sajkov D, McEvoy RD. The effects of the GABA agonist, baclofen, on sleep and breathing. *European Respiratory Journal* 1995;**8**(2):230-4.

Fra 1971 *{published data only}*

* Fra L, Bergamini L, Brignolio F, Delsedime M. [Study of the H reflex in spastic subjects treated with a GABA derivative (Ciba 34647-BA)] [Italian]. *Rivista di Neurologia* 1971;**41**(3):152-60.

Gambi 1983 *{published data only}*

* Gambi D, Rossini PM, Calenda G. Dantrolene sodium in the treatment of spasticity caused by multiple sclerosis or degenerative myelopathies: a double-blind crossover study in comparison with placebo. *Current Therapeutic Research* 1983;**33**:835-40.

Gerstenbrand 1979 *{published data only}*

* Gerstenbrand F, Lorincz A, Ludin Hp, Ringwald E. [Long-term treatment with an imidazoline derivative (DS 103--282)] [German]. *Nervenarzt* 1979;**50**(12):806-8.

Gibbins 1982 *{published data only}*

* Gibbins FJ, Lewis AM, Kesar DK. Effectiveness and safety of dantrolene sodium in comparison with baclofen in spasticity from multiple sclerosis. Cross-over study. Dantrolene sodium: New therapeutic approach to clinical problems of spasticity, Proceedings of the International Symposium. Benvenuti: Minerva Medica, 1982:59-70.

Glass 1974 *{published data only}*

* Glass A, Hannah A. A comparison of dantrolene sodium and diazepam in the treatment of spasticity. *Paraplegia* 1974;**12**(3):170-4.

Gobel 1999 *{published data only}*

* Gobel H, Schmid J, Heinze A, Pergande G. Reduction of spastic increased muscle tone in multiple sclerosis by the non-opioid analgesic flupirtine. *Schmerz* 1999;**13**(5):324-31.

Gonsette 1978 *{published data only}*

* Gonsette RE, Capart T, Demonty L. [Clinical study of sodium dantroline (Dantrium) in multiple sclerosis] [French]. *Acta Neurologica Belgica* 1978;**78**(3):141-7.

Hassan 1980 *{published data only}*

* Hassan N, McLellan DL. Double-blind comparison of single doses of DS103-282, baclofen and placebo for suppression of spasticity. *Journal of Neurology, Neurosurgery & Psychiatry* 1980;**43**(12):1132-6.

Heazlewood 1983 *{published data only}*

* Heazlewood V, Symoniw P, Maruff P, Eadie MJ. Tizanidine - initial pharmacokinetic studies in patients with spasticity. *European Journal of Clinical Pharmacology* 1983;**25**(1):65-7.

Hedley 1975 *{published data only}*

* Hedley DV, Maroun JA, Espir ML. Evaluation of baclofen (Lioresal) for spasticity in multiple sclerosis. *Postgraduate Medical Journal* 1975;**51**(599):615-8.

Herman 1992 *{published data only}*

* Herman R, D'Luzansky SC, Ippolito R. Intrathecal baclofen suppresses central pain in patients with spinal lesions. A pilot study. *The Clinical Journal of Pain* 1992;**8**(4):338-45.

Hoogstraten 1988 *{published data only}*

* Hoogstraten MC, van der Ploeg RJ, vd Burg W, Vreeling A, van Marle S, Minderhoud JM. Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. *Acta Neurologica Scandinavica* 1988;**77**(3):224-30.

Hudgson 1971 *{published data only}*

Hudgson P, Weightman D. Baclofen in the treatment of spasticity. *British Medical Journal* 1971;**4**(778):15-7.

* Hudgson P, Weightman D, Cartlidge NE. Clinical trial of baclofen against placebo. *Postgraduate Medical Journal* 1972;**48**(Suppl 5):37-40.

Huffman 1973 *{published data only}*

* Huffmann G, Fasshauer K, Giesen R. [Effects of Lioresal in therapy of spastic paralysis] [German]. *Medizinische Klinik* 1973;**68**(11):340-4.

Hugenholtz 1992 *{published data only}*

* Hugenholtz H, Nelson RF, Dehoux E, Bickerton R. Intrathecal baclofen for intractable spinal spasticity. A double-blind

crossover comparison with placebo in 6 patients. *Canadian Journal of Neurological Sciences* 1992;**19**(2):188-95.

Jabbari 1995 *{published data only}*

* Jabbari B, et al. Botulinum toxin A effectiveness against spasticity and muscle spasms. *Archives of Physical Medicine & Rehabilitation* 1995;**76**:1063 (abstr).

Jabbari 1996 *{published data only}*

* Jabbari B, Polo K, Ford G. Longterm effects of botulinum toxin A in spasticity and rigidity. *Movement Disorders* 1996;**11**(Suppl Abstract P884):234.

Jarrett 2002 *{published data only}*

* Jarrett L, Nandi P, Thompson AJ. Managing severe lower limb spasticity in multiple sclerosis: does intrathecal phenol have a role?. *Journal of Neurology, Neurosurgery & Psychiatry* 2002;**73**(6):705-9.

Jerusalem 1968 *{published data only}*

* Jerusalem F. [Double-blind study of the antispastic effect of Beta-(4-chlorphenyl)-gamma aminobutyric acid (CIBA) in multiple sclerosis [Doppeltblindstudie uber den antispastischen effekt von B-(4-chlorphenyl)-G-aminobuttersaure (CIBA) bei Multipler Sklerose]. *Der Nervenarzt* 1968;**39**(11):515-7.

Jones 1976 *{published data only}*

* Jones R, Lance J. Baclofen (Lioresal) in the long-term management of spasticity. *Medical Journal of Australia* 1976;**1**(18):654-7.

Joynt 1976 *{published data only}*

* Joynt RL. Dantrolene sodium: long-term effects in patients with muscle spasticity. *Archives of Physical Medicine & Rehabilitation* 1976;**57**(5):212-7.

Keenan 1977 *{published and unpublished data}*

* Keenan R, Kolb M, Horne M. Collaborative comparison of dantrolene sodium and diazepam in management of chronic spasticity after CNS lesions. *Clinical Therapeutics* 1977;**1**(1):48-55.

Kerty 1997 *{published data only}*

* Kerty E, Stien R. [Treatment of spasticity with botulinum toxin] [Norvegian]. *Tidsskrift for Den Norske Laegeforening* 1997;**117**(14):2022-4.

Ketelaer 1973 *{published data only}*

* Ketelaer P, Tyberghein JM, Ketelaer CJ. [C34.647-Ba (Lioresal) in the treatment of hypertonic manifestation of multiple sclerosis] [French]. *Bruxelles Medical* 1973;**53**(11):675-81.

Khan 1995 *{published data only}*

* Khan OA, Olek MJ. Clonidine in the treatment of spasticity in patients with multiple sclerosis [letter]. *Journal of Neurology* 1995;**242**(10):712-3.

Knutsson 1982 *{published data only}*

* Knutsson E, Martensson A, Gransberg L. Antiparetic and antispastic effects induced by tizanidine in patients with spastic paresis. *Journal of the Neurological Sciences* 1982;**53**(2):187-204.

Kravitz 1992 *{published data only}*

* Kravitz HM, Corcos DM, Hansen G, Penn RD, Cartwright RD, Gianino J. Intrathecal baclofen: effects on nocturnal leg muscle spasticity. *American Journal of Physical Medicine & Rehabilitation* 1992;**71**(1):48-52.

Ladd(1) 1974 *{published data only}*

* Ladd HW, Gingras G, Boucher J, Kazdan N, Keenan R. [Attenuating effect of a new pharmacological agent (Dantrolene sodium) on spasticity] [French]. *Union Medicale du Canada* 1973;**102**(5):1087-92.

Ladd(2) 1974 *{published data only}*

* Ladd H, Oist C, Jonsson B. The effect of Dantrium on spasticity in multiple sclerosis. *Acta Neurologica Scandinavica* 1974;**50**(4):397-408.

Latash 1989 *{published data only}*

* Latash ML, Penn RD, Corcos DM, Gottlieb GL. Short-term effects of intrathecal baclofen in spasticity. *Experimental Neurology* 1989;**103**(2):165-72.

Lazorthes 1990 *{published data only}*

* Lazorthes Y, Sellerin-Caute B, Verdie JC, Bastide R, Carillo JP. Chronic intrathecal baclofen administration for control of severe spasticity. *Journal of Neurosurgery* 1990;**72**(3):393-402.

Lee 1993 *{published data only}*

* Lee A, Patterson V. A double-blind study of L-threonine in patients with spinal spasticity. *Acta Neurologica Scandinavica* 1993;**88**(5):334-8.

Lee 1994 *{published data only}*

* Lee J, Harris SS, Cohen J, Cooper K, MacEwen C, Jones S. Results of a prospective randomized trial of botulinum toxin therapy in acute unilateral sixth nerve palsy. *Journal of Pediatric Ophthalmology & Strabismus* 1994;**31**(5):283-6.

Leveghi 1998 *{published data only}*

* Leveghi D, Corona AM, Bortolotti P. Intrathecal baclofen efficacy in severe spasticity: medical rehabilitative management and follow-up. *Rivista di Neurobiologia* 1998;**44**(5):499-503.

Levine 1968 *{published data only}*

* Levine IM, Jossmann PB, Friend DG, De Angelis V. Prazepam in the treatment of spasticity. A quantitative double-blind evaluation. *Neurology* 1969;**19**(5):510-6.

Levine 1969 *{published data only}*

* Levine IM, Jossmann PB, Friend DG, DeAngelis V, Kane M. Diazepam in the treatment of spasticity. *Journal of Chronic Diseases* 1969;**22**:57-62.

Levine(1) 1977 *{published data only}*

* Levine IM, Jossmann PB, Rudd J, De Angelis V. The quantitative evaluation of intravenous methocarbamol in the relief of spasticity. *Neurology* 1968;**1**(1):69-74.

Levine(2) 1977 *{published data only}*

* Levine M, Van Brocklin J. Lioresal (baclofen) treatment of spasticity: a double-blind comparison study with dantrolene. *Neurology* 1977;**27**:391.

Link 1999 *{published data only}*

* Link A, Kabus C, Haas J. Use of spasmography to assess the effects of botulinum toxin type A in patients with lower-limb spasticity. *European Journal of Neurology* 1999;**6**(Supplement 4):S69-73.

Lossius 1985 *{published data only}*

* Lossius R, Dietrichson P, Lunde PK. Effect of clorazepate in spasticity and rigidity: a quantitative study of reflexes and plasma concentrations. *Acta Neurologica Scandinavica* 1985;**71**(3):190-4.

Loubser 1991 *{published data only}*

* Loubser PG, Narayan RK, Sandin KJ, Donavan WH, Russell KD. Continuous infusion of intrathecal baclofen: long-term effects on spasticity in spinal cord injury. *Paraplegia* 1991;**29**(1):48-64.

Mai 1979 *{published data only}*

* Mai J, Pedersen E. Mode of action of dantrolene sodium in spasticity. *Acta Neurologica Scandinavica* 1979;**59**(6):309-16.

Mayer 1973 *{published data only}*

* Mayer N, Necomber SA, Herman R. Treatment of spasticity with dantrolene sodium. *American Journal of Physical Medicine* 1973;**52**(1):18-29.

Medici 1985 *{unpublished data only}*

* Medici M, Pebet M, Perez Zeinal C. Tizanidine in the treatment of spasticity. A long term study (abstract no. 20.21.02). *Journal of Neurology* 1985;**235**(Suppl):305.

Medici, M. A comparative trial of tizanidine and baclofen in patients with spasticity due to various neurological disorders (study No 39). Unpublished Sandoz Research Report.

Meinck 1989 *{published data only}*

* Meinck HM, Schonle PW, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 1989;**236**(2):120-2.

Meyler 1981 *{published data only}*

Meyler WJ, Bakker H, Kok JJ, Agoston S, Wesseling H. The effect of dantrolene sodium in relation to blood levels in spastic patients after prolonged administration. *Journal of Neurology, Neurosurgery & Psychiatry* 1981;**44**(4):334-9.

Mondrup 1983 *{published data only}*

Mondrup K, Pedersen E. The acute effect of the GABA-agonist, THIP, on proprioceptive and flexor reflexes in spastic patients. *Acta Neurologica Scandinavica* 1983;**67**(1):48-54.

Mondrup 1984 *{published data only}*

* Mondrup K, Pedersen E. The clinical effect of the GABA-agonist, progabide, on spasticity. *Acta Neurologica Scandinavica* 1984;**69**(4):200-6.

Monster 1973 *{published data only}*

* Monster AW, Herman R, Meek SS, McHenry J. Cooperative study for assessing the effects of a pharmacological agent on spasticity. *American Journal of Physical Medicine & Rehabilitation* 1973;**52**(4):163-88.

Monster 1974 *{published data only}*

* Monster, AW. Spasticity and the effect of dantrolene sodium. *Archives of Physical Medicine & Rehabilitation* 1974;**55**:373-83.

Morita 2001 *{published data only}*

* Morita H, Crone C, Christenhuis D, Petersen NT, Nielsen JB. Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. *Brain* 2001;**124**(Pt 4):826-37.

Mueller 1997 *{published data only}*

* Mueller ME, Gruenthal M, Olson WL, Olson WH. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. *Archives of Physical Medicine & Rehabilitation* 1997;**78**(5):521-4.

Muller 1987 *{published data only}*

* Muller H, Zierski J, Dralle D, Borner U, Hoffmann O. The effect of intrathecal baclofen on electrical muscle activity in spasticity. *Journal of Neurology* 1987;**234**(5):348-52.

Mutani 1971 *{published data only}*

* Mutani R, Fariello R, Quattrocolo G, Delsedime M. [Kinetometric demonstration of the antispastic action of a GABA derivative (Ciba 34647-BA)] [Italian]. *Rivista di Neurologia* 1971;**41**(3):143-51.

Nance 1995 *{published data only}*

* Nance P, Schryvers O, Schmidt B, Dubo H, Loveridge B, Fewer RD. Intrathecal baclofen therapy for adults with spinal spasticity: therapeutic efficacy and effect on hospital admissions. *Canadian Journal of Neurological Sciences* 1995;**22**(1):22-9.

Nance 1997 *{published data only}*

* Nance PW, Sheremata WA, Lynch SG, Vollmer T, Hudson S, Francis GS, et al. Relationship of the antispasticity effect of tizanidine to plasma concentration in patients with multiple sclerosis. *Archives of Neurology* 1997;**54**(6):731-6.

Neretin 1978 *{published data only}*

* Neretin VI, Kir'iakov VA, Pegova LN. [Experience using sinakten-retard in the treatment of muscular sclerosis] [Russian]. *Zhurnal Nevropatologii i Psikhiatrii Imeni S - S - Korsakova* 1978;**78**(4):514-8.

Newman 1982 *{published data only}*

Newman P. A double-blind, comparative trial of tizanidine and baclofen in the treatment of chronic spasticity in patients with multiple sclerosis (study No 27). Unpublished Sandoz Research Report 1981.

* Newman PM, Nogues M, Newnam PK, Weighman D, Hudson P. Tizanidine in the treatment of spasticity. *European Journal of Clinical Pharmacology* 1982;**23**(1):31-5.

Nielsen(1) 2000 *{published data only}*

* Nielsen JF, Anderson JB, Sinkjaer T. Baclofen increases the soleus stretch reflex threshold in the early swing phase during walking in spastic multiple sclerosis patients. *Multiple Sclerosis* 2000;**6**(2):105-14.

Nielsen(2) 2000 *{published data only}*

* Nielsen JF, Sinkjaer T. Peripheral and central effect of baclofen on ankle joint stiffness in multiple sclerosis. *Muscle & Nerve* 2000;**23**(1):98-105.

Ochs 1989 *{published data only}*

* Ochs G, Struppler A, Meyerson BA, Linderoth B, Gybels J, Gardner BP, et al. Intrathecal baclofen for long-term treatment of spasticity: a multi-centre study. *Journal of Neurology, Neurosurgery & Psychiatry* 1989;**52**(8):933-9.

Ordia 1996 *{published data only}*

* Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. *Journal of Neurosurgery* 1996;**85**(3):452-7.

Orsnes(1) 2000 *{published data only}*

* Orsnes G, Crone C, Krarup C, Petersen N, Nielsen J. The effect of baclofen on the transmission in spinal pathways in spastic multiple sclerosis patients. *Clinical Neurophysiology* 2000;**111**(8):1372-9.

Orsnes(2) 2000 *{published data only}*

* Orsnes GB, Sorensen PS, Larsen TK, Ravnborg M. Effect of baclofen on gait in spastic MS patients. *Acta Neurologica Scandinavica* 2000;**101**(4):244-8.

Pagano 1988 *{published data only}*

* Pagano M, Ferreiro M, Herskovits E. Comparative study of tizanidine and baclofen in patients with chronic spasticity. *Revista Neurologica Argentina* 1988;**14**(4):268-76.

Parke 1989 *{published data only}*

* Parke B, Penn RD, Savoy SM, Corcos D. Functional outcome after delivery of intrathecal baclofen. *Archives of Physical Medicine & Rehabilitation* 1989;**70**(1):30-2.

Patterson 1994 *{published data only}*

* Patterson V, Watt M, Byrnes D, Crowe D, Lee A. Management of severe spasticity with intrathecal baclofen delivered by a manually operated pump. *Journal of Neurology, Neurosurgery & Psychiatry* 1994;**57**(5):582-5.

Pederson 1970 *{published data only}*

* Pederson E, Arlien-Soborg P, Grynderup V, Henriksen O. GABA derivative in spasticity. (Beta-(4-chlorophenyl)-gamma-aminobulyric acid, Ciba 34.647-Ba). *Acta Neurologica Scandinavica* 1970;**46**(3):257-66.

Pederson 1981 *{published data only}*

* Pedersen E, Hansen HJ, Poulsen J. Effect of symptomatic therapy on motor difficulties in quantitative measurements of voluntary power. *Acta Neurologica Scandinavica* 1981;**64**(4):253-8.

Penders 1976 *{published data only}*

* Penders D, et al. Trial of a new muscle relaxant in the treatment of multiple sclerosis: dantrolene sodium. *Ars Medici (Nivelles)* 1976;**31**(2):331-6.

Penn 1985 *{published data only}*

* Penn Rd, Kroin Js. Continuous intrathecal baclofen for severe spasticity. *Lancet* 1985;**2**(8447):125-7.

Penn 1989 *{published data only}*

* Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke B, et al. Intrathecal baclofen for severe spinal spasticity. *New England Journal of Medicine* 1989;**320**(23):1517-21.

Penn 1992 *{published data only}*

* Penn RD. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. *Journal of Neurosurgery* 1992;**77**(2):236-40.

Perkin 1976 *{published data only}*

* Perkin GD, Aminoff MJ. A trial of brolitene in the treatment of spasticity. *British Journal of Clinical Pharmacology* 1976;**3**(5):879-882.

Petro 1980 *{published data only}*

* Petro DJ. Marijuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics* 1980;**21**(1):81-5.

Petro 1981 *{published data only}*

* Petro DJ, Ellenberger CJr. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 1981;**21**(8-9 Suppl):413S-416S.

Polman 1994 *{published data only}*

* Polman CH, Bertelsmann FW, Van Loenen Ac, Koetsier JC. 4-Aminopyridine in the treatment of patients with multiple sclerosis. Long-term efficacy and safety. *Archives of Neurology* 1994;**51**(3):292-6.

Porsasz 1981 *{published data only}*

* Porsasz G. Clinical study of Dantrium in spasticity due to multiple sclerosis [A Dantrium spasmusgatlo hatasanak klinikai vizsgalata sclerosis multiplexes betegekben]. *Ideggyogyaszati Szemle* 1981;**34**:330-6.

Reisner 1978 *{published data only}*

* Reisner H. [Pharmacological treatment of pathological increases in muscle tonus] [German]. *Wiener Medizinische Wochenschrift* 1978;**128**(3):57-62.

Ringwald 1977 *{published data only}*

* Ringwald E, Campean SJ, Gerstenbrand F, Lorincz A, Lorincz P, Ludin HP. [Clinical experiences with a new muscle relaxant (DS103-282 Sandoz)] [German] [Klinische Erfahrungen mit einem neurartigen Myotonolytikum (DS 103-282 Sandoz)]. *Nervenarzt* 1977;**48**(7):355-8.

Rodgers 1999 *{published data only}*

* Rodgers MM, Mulcare JA, King DL, Mathews T, Gupta S, Glaser RM. Gait characteristics of individuals with multiple sclerosis before and after a 6-month aerobic training

program. *Journal of Rehabilitation Research & Development* 1999;**36**(3):183-8.

Rossier 2000 *{published data only}*

* Rossier P, Van Erven S, Wade DT. The effect of magnesium oral therapy on spasticity in a patient with multiple sclerosis. *European Journal of Neurology* 2000;**7**(6):741-4.

Roussan 1982 *{published data only}*

* Roussan M, Terrence C, Fromm G. Baclofen versus diazepam for the treatment of spasticity and long-term follow-up of baclofen therapy. *Archives of Physical Medicine & Rehabilitation* 1982;**63**:503 (abstr).

Rudick 1987 *{published data only}*

* Rudick RA, Breton D, Krall RL. The GABA-agonist progabide for spasticity in multiple sclerosis. *Archives of Neurology* 1987;**44**(10):1033-6.

Saltuari 1992 *{published data only}*

* Saltuari L, Kronenberg M, Marosi MJ, Kofler M, Russegger L, Rifici C, et al. Indication, efficiency and complications of intrathecal pump supported baclofen treatment in spinal spasticity. *Acta Neurologica* 1992;**14**(3):187-94.

Smith 1991 *{published data only}*

* Smith CR, La Rocca NG, Giesser BS, Scheinberg LC. High-dose oral baclofen: experience in patients with multiple sclerosis. *Neurology* 1991;**41**(11):1829-31.

Smith 1992 *{published data only}*

* Smith MB, Brar SP, Nelson LM, Franklin GM, Cobble ND. Baclofen effect on quadriceps strength in multiple sclerosis. *Archives of Physical Medicine & Rehabilitation* 1992;**73**(3):237-40.

Toste 1999 *{published data only}*

* Toste T, Balao F, Festas C, Pereira S, Marcal N. Treatment of spasticity with intrathecal morphine in multiple sclerosis. *Arquivos de Fisiatria e Doencas Osteo-Articulares* 1999;**6**(2):63-9.

Ungerleider 1987 *{published data only}*

* Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Advances in Alcohol & Substance Abuse* 1987;**7**(1):39-50.

van Ouwenaller 1985 *{published data only}*

* van Ouwenaller C, Chantraine A. A new myorelaxant in neurological affectations. *Journal of Neurology* 1985;**235**(Suppl):305.

Verrier 1977 *{published data only}*

* Verrier M, Ashby P, MacLeod S. Diazepam effect on reflex activity in patients with complete spinal lesions and in those with other causes of spasticity. *Archives of Physical Medicine & Rehabilitation* 1977;**58**(4):148-53.

Vogt 2000 *{published data only}*

* Vogt T, Urban PP. Optimising therapy of spastic syndrome by combining intrathecal baclofen with botulinum toxin. *Nervenarzt* 2000;**71**(12):1007-11.

Weiser 1978 *{published data only}*

* Weiser R, Terenty T, Hudgson P, Weightman D. Dantrolene sodium in the treatment of spasticity in chronic spinal cord disease. *The Practitioner* 1978;**221**(1321):123-7.

Wickstrom 1987 *{published data only}*

* Wickstrom J. A double-blind, parallel group, therapeutic comparative study to assess the efficacy and tolerability of tizanidine (Sirdalud) vs baclofen in the treatment of spasticity due to multiple sclerosis. Unpublished Sandoz Research Report 1987.

Wilson 1966 *{published data only}*

* Wilson LA, McKechnie AA. Oral diazepam in the treatment of spasticity in paraplegia: a double-blind trial and subsequent impressions. *Scottish Medical Journal* 1966;**11**(2):46-51.

Additional references

Ashworth 1964

Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner* 1964;**192**:540-2.

Bohannon 1987

Bohannon RW. Variability and reliability of the pendulum test for spasticity using a Cybex isokinetic dynamometer. *Physical Therapy* 1987;**67**(5):659-61.

Clarke 1995

Clarke M, Oxman AD, editors. Establishing and maintaining an international register of RCTs. Cochrane Reviewers' Handbook. In: The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration. Oxford: Update Software; 1995.

Haber 1985

Haber A, LaRocca N (eds). Minimal record of disability for multiple sclerosis. New York: National Multiple Sclerosis Society, 1985.

Kurtzke 1983

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**(11):1444-52.

Lance 1980

Lance JW. Symposium synopsis. Spasticity: disordered motor control. Miami: Symposia Specialists, 1980:485-94.

Pandyan 1999

Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clinical Rehabilitation* 1999;**13**(5):373-83.

Perry 1993

Perry J. Determinants of muscle function in the spastic lower extremity. *Clinical Orthopaedics and Related Research* 1993;**288**:10-26.

Poser 1983

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology* 1983;**13**(3):227-31.

Wade 1992

Wade DT. Measurement in neurological rehabilitation. Oxford: Oxford Medical Publications, 1992.

Wallace 1994

Wallace JD. Summary of combined clinical analysis of controlled clinical trials with tizanidine. *Neurology* 1994;**44**(11 Suppl 9):S60-8; discussion S68-9.

Whitehead 1994

Whitehead A, Jones NM. A meta-analysis of clinical trials involving different classifications of response into ordered categories. *Statistics in Medicine* 1994;**13**(23-4):2503-15.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Basmajian 1974

Methods	Crossover study
Participants	8 patients
Interventions	Baclofen (dose not reported) v. placebo
Outcomes	Resistance to passive stretch, range of motion, reflexes, clonus, associated movements, muscle power (clinically and by strain gauge), patellar reflex force, quadriceps EMG, patient self-report of spasms and function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Basmajian 1975

Methods	Crossover study (same methodology as Basmajian 1974)
Participants	22 MS patients (8 patients previously reported in Basmajian 1974)
Interventions	Baclofen (dose not reported) v. placebo
Outcomes	Resistance to passive stretch, range of motion, reflexes, clonus, associated movements, muscle power (clinically and by strain gauge), patellar reflex force, quadriceps EMG, patient self-report of spasms and function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Basmajian 1984

Methods	Crossover studies, with four arms comparing high and low doses of drugs
Participants	Total 30 patients in the two studies (Basmajian 1984 & 1986)
Interventions	Ketazolam (30mg & 60mg) v. diazepam (15mg & 30mg)
Outcomes	Muscle tone & power, range of motion, reflexes, clonus, associated movements, pain, spasms, subjective impression of level of function, patellar reflex force, quadriceps EMG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Basmajian 1986

Methods	see Basmajian1984 for combined summary
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Bass 1988

Methods	Crossover study
Participants	66 patients
Interventions	Baclofen (up to 80mg) v. tizanidine (up to 32mg)
Outcomes	Muscle tone & power, EDSS score, Pedersen functional disability scale, reflexes, clonus, overall evaluations of efficacy and tolerability
Notes	

Risk of bias

Bass 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bovier 1985

Methods	
Participants	
Interventions	Progabide v. placebo
Outcomes	
Notes	Omitted from review as drug not used therapeutically

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Brar 1991

Methods	Crossover study with 5 stages.
Participants	30 patients with minimal to moderate spasticity
Interventions	Baclofen (20mg) or placebo, with and without an exercise programme.
Outcomes	Ashworth, Cybex II isokinetic unit, timed gait, patient questionnaire.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Chrzanowski 1981

Methods	Parallel-group study
Participants	23 MS patients aged 24-69
Interventions	Baclofen (up to 90mg) v. tizanidine (up to 36mg)
Outcomes	Ashworth score, spasm & clonus score, functional assessment - no details reported for any of these assessments

Chrzanowski 1981 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Eyssette 1988

Methods	Multi-centre, parallel-group study
Participants	100 patients aged 18-70
Interventions	Baclofen (up to 60mg) v. tizanidine (up to 24mg)
Outcomes	Locomotor function, condition in bed & chair, spasms, tonic stretch reflex, clonus, power, bladder control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Feldman 1978

Methods	Crossover study
Participants	23 patients aged 38-53 with any degree of spasticity
Interventions	Baclofen (up to 80mg) v. placebo
Outcomes	Daily spasm count, resistance to passive movement, clonus, Barthel score.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

From 1975

Methods	Crossover study
Participants	16 mostly non-ambulant patients

From 1975 *(Continued)*

Interventions	Baclofen (up to 120mg) v. diazepam (up to 40mg)
Outcomes	Ashworth score, clonus, spasm score, walking ability, side-effects, physician's global assessment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gelenberg 1973

Methods	Crossover trial
Participants	20 patients (14 ambulant)
Interventions	Dantrolene (up to 800mg) v. placebo
Outcomes	Resistance to passive movement, clonus, reflexes
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Grazko 1995

Methods	Crossover study
Participants	5 patients
Interventions	Botulinum toxin (dose estimated according to muscle size) v. placebo
Outcomes	Ashworth score, spasm score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hauser 1992

Methods	Crossover trial
Participants	26 ambulant patients with spasticity or spasms which affected function
Interventions	Threonine (7.5g) v. placebo
Outcomes	Ashworth scale, EDSS score, Ambulation Index, combined clinical assessment scale, patient scale of three most troublesome symptoms, video gait analysis, H-reflex study
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Hyman 2000

Methods	Multi-centre, parallel-group, dose-ranging study
Participants	74 patients with disabling thigh-adductor spasticity
Interventions	Botulinum toxin (Dysport) 500, 1000 or 1500 MU v. placebo
Outcomes	Joint range of movement, total spasticity score (modified Ashworth score x spasm score), pain, hygiene, overall clinical impression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jellinger 1983

Methods	Cross-over study
Participants	32 MS patients aged 18-70
Interventions	Tizanidine (up to 24mg, mean 14.8mg) v. diazepam (up to 30mg, mean 14.5mg)
Outcomes	Kurtzke EDSS, Pedersen functional assessment scale, global impression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Jellinger 1983 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Joder-Ohlenbusch '84

Methods	Cross-over study (6 week treatment periods)
Participants	30 patients, 25 with MS (individual patient data available)
Interventions	Vigabatrin 3 g daily v. placebo
Outcomes	Ashworth score, unvalidated spasm score
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Killestein 2002

Methods	Cross-over study (4 week treatment periods)
Participants	16 MS patients
Interventions	2.5-5mg THC v. C. sativa plant extract v. placebo
Outcomes	Ashworth score, EDSS, MS Functional composite score (timed walk, 9 hole peg test, PASAT), MS Fatigue Severity Scale, SF36, visual analogue scales
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Lapierre 1987

Methods	Parallel-group trial
Participants	66 patients aged 18-60, with spasticity severe enough to affect function
Interventions	Tizanidine (up to 36mg) v. placebo
Outcomes	Resistance to passive stretch, muscle power, reflexes, clonus, EDSS score, ambulation index, upper extremities index, electrophysiological studies (including H-max/M-max)

Lapierre 1987 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Levine(1) 1969

Methods	Crossover study
Participants	18 mainly non-ambulant, paraplegic patients
Interventions	Prazepam (5-25mg as tolerated) v. placebo
Outcomes	EMG (spontaneous muscle activity, and response to electrical stimuli and gravity)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Luisto 1982

Methods	
Participants	Included 3 MS patients
Interventions	Dantrolene (up to 400mg daily) v. placebo
Outcomes	Unvalidated spasticity scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pellkofer 1989

Methods	Parallel-group study lasting up to 35 days
Participants	47 MS patients with disabling lower limb spasticity

Pellkofer 1989 *(Continued)*

Interventions	Tetrazepam v. tizanidine v. baclofen (doses optimised but not reported)
Outcomes	EDSS, Ashworth scale, symptom reports, unvalidated 4-point scale of tolerability and 5-point scale of overall therapeutic effect
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rinne 1980

Methods	Parallel-group studies (two were excluded from the review as results for MS and non-MS patients could not be separated)
Participants	30 patients
Interventions	Tizanidine (up to 18mg) v. diazepam (up to 22.5mg)
Outcomes	Ashworth score, overall tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sachais 1977

Methods	Parallel-group study
Participants	106 patients
Interventions	Baclofen (60-80mg) v. placebo
Outcomes	Resistance to passive movement, spasms, degree of knee jerks, subjective patient report of spasms, clonus and function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sawa 1979

Methods	Crossover study
Participants	21 patients with lower limb spasticity
Interventions	Baclofen (up to 60mg) v. placebo
Outcomes	Time taken for passively flexed knee of a supine patient to fall on to the bed, spasms & gait.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schmidt 1975

Methods	Crossover study, with four arms comparing low and high doses of drugs
Participants	46 mainly ambulant patients with moderate to severe spasticity which affected function but without severe lower limb weakness
Interventions	Diazepam (8mg and 20mg) v. dantrolene (100mg and 300 mg)
Outcomes	Muscle tone & power, coordination, reflexes, clonus, walking-speed, adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sheplan 1975

Methods	Crossover study
Participants	8 men
Interventions	Dantrolene (up to 400mg) v. placebo
Outcomes	Resistance to passive movement, clonus, reflexes, stretch reflex inhibition, H-reflex response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Sheplan 1975 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Smith 1994

Methods	Multi-centre, parallel-group study
Participants	220 patients aged 18-70
Interventions	Tizanidine (2-36mg) v. placebo
Outcomes	Primary end-points: Ashworth score, patient diaries (muscle spasm & clonus scores). Secondary end-points: reflexes, clonus, spasms (assessed by physician), muscle power (MRC grade), walking time, ADL, global evaluation of efficacy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Smolenski 1981

Methods	Parallel-group trial
Participants	21 hospitalised patients aged 42-73
Interventions	Baclofen (up to 80mg) v. tizanidine (up to 36mg)
Outcomes	Ashworth scale, EDSS score, spasm score, muscle power, global impression, side-effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Snow 1990

Methods	Crossover study
Participants	10 severely-disabled patients with adductor spasticity inadequately treated on oral medication
Interventions	Botulinum toxin (supplied by Smith-Kettlewell Eye Research Institute, San Francisco) 400 MU v. placebo
Outcomes	Muscle tone, spasm frequency, hygiene score

Snow 1990 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Stien 1987

Methods	Parallel-group trial
Participants	40 severely handicapped patients
Interventions	Baclofen (up to 90mg) v. tizanidine (up to 36 mg)
Outcomes	Ashworth scale, EDSS, Pedersen rating scales, overall impression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tell 1981

Methods	Cross-over trial (duration of each arm 5-14 days)
Participants	10 patients, 5 with MS (individual patient data available)
Interventions	Vigabatrin 2 g daily v. placebo
Outcomes	Unvalidated spasticity and spasm scores
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tolosa 1975

Methods	Parallel-group study
Participants	23 patients (11 wheelchair-bound)

Tolosa 1975 *(Continued)*

Interventions	Dantrolene (up to 800mg) v. placebo
Outcomes	Resistance to passive movement, reflexes, clonus
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

UKTTG 1994

Methods	Multi-centre, parallel-group study
Participants	187 patients aged 18-75
Interventions	Tizanidine (up to 36mg) v. placebo
Outcomes	Primary outcome measure: Ashworth scale. Secondary measures: muscle power (MRC grade), EDSS score, reflexes, clonus, spasm score, 8m walking time, scales of intermediate motor skills and upper limb functions, ADL (Incapacity Status Scale), subjective assessments of overall effect on function, efficacy and tolerability
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wade 2003

Methods	Crossover study with 2 week blocks, without intervening washout periods
Participants	24 patients with intractable neurogenic symptoms, 18 with MS
Interventions	THC v. CBD v. 1:1 mixture of THC:CBD v. placebo
Outcomes	daily patient visual analogue scales, Ashworth score, numerical investigator rating of symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Wuthrich 1981

Methods	6 week parallel-group study
Participants	20 MS patients aged 19-71
Interventions	Baclofen (20-60mg) v. tizanidine (8-24mg)
Outcomes	As Chrzanowski (1981)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ADL:
Ashworth:
CBD:
Cybex II isokinetic unit:
EDSS:
EMG:
MRC grade:
PASAT:
THC:

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abel 1994	Not RCT of sufficient duration
Anonymous 1973	Not RCT of sufficient duration
Anonymous 1974	Not RCT of sufficient duration
Azouvi 1996	Not RCT of sufficient duration
Barat 1974	Not a randomised controlled trial
Barbeau 1982	Not RCT of sufficient duration
Basmajian 1973	Unable to extract data for non-MS patients
Baykuschev 1968	Not RCT of sufficient duration
Becker 1995	Not RCT of sufficient duration
Behan 1982	Not RCT of sufficient duration
Bergamini 1966	Not a randomised controlled trial
Bianchi 1999	Not RCT

Study	Reason for exclusion
Birkmayer 1967	Not RCT
Bittencourt 1988	Not RCT of sufficient duration
Broggi 1993	Not RCT of sufficient duration
Broseta 1989	Not RCT of sufficent duration
Burke 1971	Not RCT of sufficient duration
Cartlidge 1974	Unable to separate data for non-MS patients
Castaigne 1973	Not a randomised controlled trial
Cendrowski(1) 1977	Not RCT of sufficient duration
Cendrowski(2) 1977	Not RCT of sufficient duration
Chantraine 1980	Not RCT of sufficient duration
Chipman 1974	Not RCT of sufficient duration
Chyatte 1971	Not RCT of sufficient duration
Coffey 1993	Not RCT of sufficient duration
Cohan 1980	Not RCT of sufficient duration
Corston 1981	Unable to separate non-MS patients
Cumming 1972	Not RCT of sufficient duration
Cutter 2000	Not RCT of sufficient duration
Dressnandt 1996	Not RCT of sufficient duration
Duncan 1976	Unable to separate data for non-MS patients
Dunevsky 1998	Not an RCT
Emre 1994	Not RCT of sufficient duration
Finnimore 1995	Not relevant to this review
Fra 1971	Not a randomised controlled trial
Gambi 1983	Unable to extract data for non-MS patients
Gerstenbrand 1979	Not an RCT
Gibbins 1982	No evidence of blinding in published report
Glass 1974	Not RCT of sufficient duration
Gobel 1999	Not RCT of sufficient duration

Study	Reason for exclusion
Gonsette 1978	Not RCT of sufficient duration
Hassan 1980	Not RCT of sufficient duration.
Heazlewood 1983	Not RCT of sufficient duration
Hedley 1975	Not RCT of sufficient duration.
Herman 1992	Unable to separate data for non-MS patients.
Hoogstraten 1988	Single-blind study only
Hudgson 1971	Unable to separate data for non-MS patients
Huffman 1973	Not RCT of sufficient duration
Hugenholtz 1992	Unable to separate data for non-MS patients
Jabbari 1995	Not RCT of sufficient duration
Jabbari 1996	Not RCT of sufficient duration
Jarrett 2002	Not RCT
Jerusalem 1968	Not RCT
Jones 1976	Not RCT of sufficient duration
Joynt 1976	Not RCT of sufficient duration
Keenan 1977	Unable to separate data for non-MS patients
Kerty 1997	Not RCT of sufficient duration
Ketelaer 1973	Not a randomised controlled trial
Khan 1995	Not RCT of sufficient duration
Knutsson 1982	Not RCT of sufficient duration
Kravitz 1992	Not RCT of sufficient duration.
Ladd(1) 1974	Not RCT of sufficient duration
Ladd(2) 1974	Not RCT of sufficient duration.
Latash 1989	Not RCT of sufficient duration
Lazorthes 1990	Not RCt of sufficient duration
Lee 1993	Unable to separate non-MS patients
Lee 1994	Not relevant to this review
Leveghi 1998	Not RCT

Study	Reason for exclusion
Levine 1968	Not RCT of sufficient duration
Levine 1969	Not RCT
Levine(1) 1977	Unable to separate data for non-MS patients
Levine(2) 1977	Not RCT of sufficient duration
Link 1999	Not RCT
Lossius 1985	Not RCT of sufficient duration
Loubser 1991	Not MS patients
Mai 1979	Not RCT of sufficient duration
Mayer 1973	Not RCT of sufficient duration
Medici 1985	Unable to separate non-MS patients
Meinck 1989	Not RCT of sufficient duration
Meyler 1981	Not RCT of sufficient duration
Mondrup 1983	Not RCT of sufficient duration
Mondrup 1984	Drug not used therapeutically for toxicity
Monster 1973	Unable to separate data for non-MS patients
Monster 1974	No details of patients' diagnoses. No validated outcome measure used. Unable to extract details of first crossover period
Morita 2001	Not RCT
Mueller 1997	Not RCT of sufficient duration
Muller 1987	Not RCT of sufficient duration
Mutani 1971	Not a randomised controlled trial
Nance 1995	Not RCT of sufficient duration
Nance 1997	Not relevant to this review
Neretin 1978	Not RCT of sufficient duration
Newman 1982	Unable to separate data for non-MS patients
Nielsen(1) 2000	Not RCT
Nielsen(2) 2000	Not RCT
Ochs 1989	Not RCT of sufficient duration

Study	Reason for exclusion
Ordia 1996	Not RCT of sufficient duration
Orsnes(1) 2000	Not RCT
Orsnes(2) 2000	Not RCT
Pagano 1988	Unable to separate data for non-MS patients
Parke 1989	Not RCT of sufficient duration
Patterson 1994	Not RCT of sufficient duration
Pederson 1970	Not RCT of sufficient duration
Pederson 1981	Not RCT of sufficient duration.
Penders 1976	Not RCT of sufficient duration.
Penn 1985	Not RCT of sufficient duration.
Penn 1989	Not RCT of sufficient duration.
Penn 1992	Not RCT of sufficient duration.
Perkin 1976	Drug not used therapeutically for toxicity
Petro 1980	Not RCT of sufficient duration.
Petro 1981	Not RCT of sufficient duration.
Polman 1994	Not RCT of sufficient duration
Porsasz 1981	Not a randomised controlled trial
Reisner 1978	Not a randomised controlled trial
Ringwald 1977	Not RCT
Rodgers 1999	Not RCT
Rossier 2000	Not RCT
Roussan 1982	Unable to separate data for non-MS patients
Rudick 1987	Drug not used therapeutically for toxicity
Saltuari 1992	Not RCT of sufficient duration
Smith 1991	Not RCT of sufficient duration
Smith 1992	Not RCT of sufficient duration
Toste 1999	Not RCT
Ungerleider 1987	Not RCT of sufficient duration

Study	Reason for exclusion
van Ouwenaller 1985	Not MS patients
Verrier 1977	Not RCT of sufficient duration
Vogt 2000	Not RCT
Weiser 1978	Unable to separate data for non-MS patients
Wickstrom 1987	Unable to obtain further details of study
Wilson 1966	Unable to separate data for non-MS patients

APPENDICES

Appendix 1. CENTRAL search strategy

#1"multiple sclerosis"
#2MeSH descriptor Multiple Sclerosis explode all trees
#3"transverse myelitis"
#4MeSH descriptor Myelitis, Transverse, this term only
#5"neuromyelitis optica"
#6"optic neuritis"
#7MeSH descriptor Optic Neuritis explode all trees
#8"encephalomyelitis acute disseminated"
#9MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only
#10"devic"
#11MeSH descriptor Muscle Spasticity explode all trees
#12MeSH descriptor Spasm explode all trees
#13spasticity
#14spasm
#15muscle NEXT spasticity
#16(#11 OR #12 OR #13 OR #14 OR 25)
#17MeSH descriptor Baclofen, this term only
#18MeSH descriptor Dantrolene explode all trees
#19MeSH descriptor Botulinum Toxins explode all trees
#20baclofen
#21dantrolene
#22tizanidine
#23gabapentin
#24botulinum NEXT toxin
#25(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#26MeSH descriptor Vigabatrin, this term only
#27MeSH descriptor gamma-Aminobutyric Acid explode all trees
#28MeSH descriptor Diazepam explode all trees
#29vigabatrin
#30diazepam
#31ketazolam
#32(#26 OR #27 OR #28 OR #29 OR #30 OR #31)
#33MeSH descriptor Cannabinoids explode all trees
#34MeSH descriptor Aminopyridines explode all trees
#35cannabinoid*
#36cyproheptadine
#37progabide
#38oxcarbazepine
#39threonine

#40diaminopyridine
#41GABA
#42(#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41)
#43(#16 AND (#25 OR #32 OR #42))
#44MeSH descriptor Demyelinating Diseases, this term only
#45"demyelinating disease*"
#46(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #44 OR #45)
#47(#43 AND #46)

Appendix 2. MEDLINE (PubMed) search strategy

((("Muscle Spasticity"[Mesh]) OR ("Spasm"[Mesh]) OR (spasticity) OR (spasm) OR ("muscle spasticity")) AND ((("Baclofen"[Mesh]) OR ("Dantrolene"[Mesh]) OR ("Botulinum Toxins"[Mesh]) OR (baclofen) OR (dantrolene) OR (tizanidine) OR (gabapentin) OR ("botulinum toxin*")) OR (("Vigabatrin"[Mesh]) OR ("gamma-Aminobutyric Acid"[Mesh]) OR ("Diazepam"[Mesh]) OR (vigabatrin) OR (diazepam) OR (ketazolam)) OR (("Cannabinoids"[Mesh]) OR ("Aminopyridines"[Mesh]) OR (cannabinoid*) OR (cyproheptadine) OR (progabide) OR (oxcarbazepine) OR (threonine) OR (diaminopyridine) OR (GABA)))) AND ((((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis"))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh])))))

Appendix 3. EMBASE search strategy

((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelooptic neuropathy'/exp) OR ('multiple sclerosis':ab,ti) OR ('neuromyelitis optica':ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ab,ti)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('randomized controlled trial'/exp) OR (random**:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo*:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign*:ab,ti) OR (allocat*:ab,ti) OR (volunteer*:ab,ti))) AND (('spasticity'/exp) OR ('muscle spasm'/exp) OR (spasticity:ab,ti) OR (spasm:ti,ab)) AND (('baclofen'/exp) OR ('dantrolene'/exp) OR ('botulinum toxin'/exp) OR (baclofen:ab,ti) OR (dantrolene:ab,ti) OR ('botulinum toxins':ab,ti) OR (tizanidine:ab,ti) OR (gabapentin:ab,ti) OR ('vigabatrin'/exp) OR (vigabatrin:ab,ti) OR ('4 aminobutyric acid'/exp) OR ('diazepam'/exp) OR (diazepam:ab,ti) OR (ketazolam:ab,ti) OR (cannabinoid*:ab,ti) OR ('cannabinoid'/exp) OR (cyproheptadine:ab,ti) OR (progabide:ab,ti) OR (oxcarbazepine:ab,ti) OR (threonine:ab,ti) OR (diaminopyridine:ab,ti) OR ('aminopyridine derivative'/exp) OR (gaba:ab,ti)) AND [humans]/lim AND [embase]/lim

WHAT'S NEW

Date	Event	Description
30 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 2000

Date	Event	Description
1 June 2003	New search has been performed	Searches were re-run
1 June 2003	New citation required but conclusions have not changed	Substantive amendment
15 June 2001	New citation required but conclusions have not changed	Substantive amendment
15 June 2001	New search has been performed	Searches were-re-run

CONTRIBUTIONS OF AUTHORS

All three reviewers contributed to the design of the protocol, assessment of studies, extraction of data and writing of the review.

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Dyskinesia Agents [therapeutic use]; Botulinum Toxins [therapeutic use]; Multiple Sclerosis [*complications]; Muscle Relaxants, Central [*therapeutic use]; Muscle Spasticity [*drug therapy] [etiology]; Randomized Controlled Trials as Topic

MeSH check words

Humans