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Pharmacological interventions for spasticity following spinal cord injury (Review)

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[Intervention Review]

Pharmacological interventions for spasticity following spinal cord injury

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ABSTRACT

Background

Spasticity is a major health problem for patients with a spinal cord injury (SCI). It limits their mobility and affects their independence in activities of daily living (ADL) and work. Spasticity may also cause pain, loss of range of motion, contractures, sleep disorders and impair ambulation in patients with an incomplete lesion. The effectiveness of available drugs is still uncertain and they may cause adverse effects. Assessing what works in this area is complicated by the lack of valid and reliable measurement tools. The aim of this systematic review is to critically appraise and summarise existing information on the effectiveness of available treatments, and to identify areas where further research is needed.

Objectives

To assess the effectiveness and safety of baclofen, dantrolene, tizanidine and any other drugs for the treatment of long-term spasticity in SCI patients, as well as the effectiveness and safety of different routes of administration of baclofen.

Search methods

We searched the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE/PubMed, EMBASE, Zetoc, Web of Knowledge, CINAHL and Current Controlled Trials. We also checked the reference lists of relevant papers to identify any further studies. The searches were last conducted in July 2008.

Selection criteria

All parallel and cross-over randomised controlled trials (RCTs) including spinal cord injury patients complaining of 'severe spasticity'. Studies where less than 50% of patients had a spinal cord injury were excluded.

Data collection and analysis

Methodological quality of studies (allocation concealment, blinding, patient's characteristics, inclusion and exclusion criteria, interventions, outcomes, losses to follow up) was independently assessed by two investigators. The heterogeneity among studies did not allow quantitative combination of results.

Main results

Nine studies met the inclusion criteria. Study designs were: 8 cross-over and 1 parallel-group trial. Two studies (14 SCI patients), showed a significant effect of intrathecal baclofen in reducing spasticity (Ashworth Score and ADL performances), compared to placebo, without any adverse effects. The study comparing tizanidine to placebo (118 SCI patients) showed a significant effect of tizanidine in improving Ashworth Score but not in ADL performances. The tizanidine group reported significant rates of adverse effects (drowsiness, xerostomia).

For the other drugs (gabapentin, clonidine, diazepam, amytal and oral baclofen) the results did not provide evidence for clinically significant effectiveness.

Authors' conclusions

There is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care.

PLAIN LANGUAGE SUMMARY

Not enough evidence about the effects of drugs used to try and reduce spasticity in the limbs after spinal cord injury

A major problem after spinal cord injury is muscle resistance to having the arms or legs moved (spasticity). There can also be spasms. This can severely limit a person's mobility and independence, and can cause pain, muscle problems, and sleep difficulties. Treatments to try and reduce spasticity include exercise, and drugs to try and decrease the muscle tone. The review found there was not enough evidence from trials to assess the effects of the range of drugs used to try and relieve spasticity after spinal cord injury. The authors of the review call for more research and make recommendations as to how this research should be conducted.

BACKGROUND

Spasticity is a major health problem for patients with a spinal cord injury (SCI). In a study reporting the incidence of spasticity one year after SCI, 67% of patients had developed spasticity associated with involuntary uncontrolled movements (spasms), 37% received antispastic medication, and 11% failed to respond to the treatment (Maynard 1990).

In a database of self-reported secondary medical problems, 99 SCI patients reported spasticity as the main complication (53%), followed by pain (44%), and pressure ulcers (38%) (Walter 2002). The prevalence of secondary impairments in long standing SCI has been studied on 482 individuals via a mailed questionnaire. Spasticity was the second most reported complication (40%) after urinary tract infections. Spasticity was more frequent in patients with quadriplegia and in cases with incomplete lesion (Frankel B and C). Moreover, there was a significant association between the occurrence of secondary impairment and perceived health status and personal income (Noreau 2000).

Spasticity severely limits patients' mobility and positioning, and affects independence in activities of daily living (ADL) and work. Spasticity may also cause pain, loss of range of motion, contractures, sleep disorders and impaired ambulation in patients with an incomplete lesion. The usual approach to treating spasticity relies on trying to decrease muscle tone with physical exercises and medication (baclofen, dantrolene sodium, diazepam, clonidine) used as monotherapy or in combination.

More recently, new medications have been proposed (tizanidine, cannabinoid (Campbell 2001), 4-aminopyridine (Donovan 2000), botulinum toxin (Richardson 2000)), as well as older drugs (i.e. baclofen) via new administration routes such as an implanted intrathecal pump (Creedon 1997). The effectiveness of these drugs is still uncertain and they may cause adverse effects. Assessing what works in this area is further complicated by the lack of valid and reliable measurement tools able to capture the whole spectrum of impairment caused by the condition, rather than just assessing the severity of spasticity (Priebe 1996).

Why it is important to do this review

The aim of this systematic review is to critically appraise and summarise existing information of the effectiveness of available treatments and to identify areas where further research is needed.

OBJECTIVES

The objectives of this review are:

- to assess the effectiveness and safety of drugs used for the treatment of long-term spasticity in SCI patients versus no treatment or placebo;
- to assess the comparative effectiveness of different antispastic drugs;
- to assess the effectiveness and safety of different routes of administration of baclofen.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials. Cross-over studies to be included only if the sequence of treatment allocation was randomly allocated. No language restriction has been applied.

Types of participants

Patients of either sex, any age, with complete or incomplete spinal cord injury at any level complaining of severe spasticity defined as 'a motor disorder characterized by a velocity-dependent increase in tonic stretch reflex (muscle tone) with abnormal spinal reflexes, clonus and muscle spasms' (Katz 1989).

Severity has been classified where possible using the modified Ashworth scale (Bohannon 1987) where patients with a score between three and five are considered to have 'severe disease'.

Studies which included patients who did not have a spinal cord injury have only been considered if the proportion of patients with SCI exceeded 50%.

Types of interventions

- Comparison of any antispastic drug versus no treatment or placebo.
- Comparison of one antispastic drug with another.
- Comparison of different routes of administration and different duration of treatment.

Types of outcome measures

- Severity of spasticity using the Ashworth scale (standard or modified) or other measures, such as the pendulum test.
- Frequency and severity of spasms (i.e. Penn spasm score).
- Pain (i.e. visual analogue scales).
- Functional status in terms of ability to perform both primary and extended activities of daily living (ADL) and on work related activities using a disability scale (i.e. Barthel index, Klein-Bell scale etc.).
- Adverse effects of drugs (drowsiness, confusion, hypotension, reduction of muscular strength) and surgical procedures (dislodgement of catheters, failure of pump, pain in the implantation site etc.).
- Economic evaluation with outcomes of cost/effectiveness, resource consumption etc.
- Quality of life (QoL) measured with scales or reported with outcomes, such as return to work or level of social and recreational activities.

Search methods for identification of studies

Searches were not restricted by date, language or publication status.

Electronic searches

We searched the following electronic databases:
•Cochrane Injuries Group Specialised Register (to July 2008);
•CENTRAL (*The Cochrane Library* to Issue 3, 2008);
•MEDLINE (1950 to July [week 1] 2008);

•PubMed (searched to 15 July 2008 [last 5 years]);
•EMBASE (1980 to July 2008);
•Current Controlled Trials Meta Register of trials [http://www.controlled-trials.com/mrct/] (searched 15 July 2008);
•CINAHL (1982 to July 2008);
•Web of Knowledge; Science Citation Index [expanded] (to 15 July 2008);
•Zetoc (searched 16 July 2004 to 2008).

The full search strategies are listed in Appendix 1.

Searching other resources

In addition, reference lists of relevant articles were checked and experts in the area were contacted, as were drug companies marketing antispastic medications.

Data collection and analysis

Selection of studies

Abstracts of all studies identified through electronic searching were scanned by two review authors and the full text of relevant articles were retrieved.

Two review authors independently assessed the identified studies for eligibility. Any disagreement was discussed with the other member of the working group until agreement was reached.

Data extraction and management

Data were extracted from each study, using a data extraction form developed to collect the following information: type of study design (cross-over, parallel), method of randomisation, blinding, number of participants randomised to each group, general characteristics of patients, inclusion and exclusion criteria, interventions, outcomes measured, and number of participants lost to follow up.

Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Schultz 1995), two reviewers scored this quality on the scale used by Higgins (Higgins 2008) as shown below, assigning 'Yes' to best quality and 'No' to the poorest:

- Yes: trials deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment);
- Unclear: trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories;
- No: trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

RESULTS

Description of studies

The searches have retrieved a total of 262 references to date. Nine trials met the inclusion criteria. Eight were cross-over trials and one a parallel group trial. Three out of the eight cross-over studies compared intrathecal baclofen to saline placebo (Penn 1989; Hugenholtz 1992; Kravitz 1992), one clonidine to placebo (Stewart 1991), one gabapentin to placebo (Gruenthal 1997), one Valium to Amytal and to placebo (Corbett 1972) and two compared baclofen to placebo (Jones 1970; Burke 1971). These two papers were duplicate reports of the same study population and have thus been considered as one study in this review (Burke 1971). The parallel group trial compared tizanidine to placebo (Nance 1994).

Two out of three studies of intrathecal baclofen (Penn 1989; Hugenholtz 1992) had a 'preliminary phase', in which bolus doses of baclofen were infused into the lumbar intrathecal space to determine the response to the medication, to observe any adverse effects and gauge the individual sensitivity to the drug (optimal individual dose). The third study of intrathecal baclofen (Kravitz 1992) did not have any preliminary phase as six of the patients were from the Penn 1989 study with an active pump already implanted. In this study the aim was to evaluate the effect of baclofen infusion on sleep disturbances due to spasticity.

One study included patients undergoing an antispastic treatment with baclofen (15 patients), diazepam (11 patients), dantrolene (three patients), clonazepam (two patients), and clonidine (one patient) (Gruenthal 1997).

a) Cross-over studies

The number of patients enrolled in the eight cross-over studies was 100 (80 males), with an age range of 16 to 62 years; in one trial (Corbett 1972), age was not reported. Eighty-six patients had a spinal cord injury lesion and 14 had multiple sclerosis. Information on the level of lesion was available for 50 patients: 28 were quadriplegic and 22 paraplegic. Completeness of lesion is reported for 46 patients: 25 had a complete lesion, 21 had an incomplete lesion. Only Stewart 1991 defined the type of lesion according to the Frankel classification. Most of the participants were patients suffering from long-standing spasticity with severe disabling spasms uncontrolled by medication (time from onset ranged from 1 to 20 years). Information on functional status in terms of ability to perform both primary and extended ADL and information about lifestyles was not reported in most of the studies. Only Hugenholtz 1992 reported that patients were independent on transfers at least from wheelchair, while Penn 1989 reported all patients were dependent on ADL.

Outcomes, which were usually assessed at baseline and at the end of the study, were as follows:

- Ashworth score or similar 5 or 6-point scale (1 to 5 or 0 to 5) in six trials;
- spasm score (0 to 4) in two trials; one study recorded frequency of spasm via patient interview;
- neurological examination including at least one of the following: reflex, induced spasm, muscle strength, clonus. High variability was found with two studies reporting a reflex score of 0 to 4, two studies reporting a clonus score of 0 to 3, and three studies reporting a muscle strength score of 1 to 5;
- EMG recording and neurophysiological study in five trials; in one study this was the only outcome measure;
- subjective evaluation of spasticity was tested in two studies (Stewart 1991; Gruenthal 1997), using a six-point analogue Likert scale in which spasms were rated from 'none' to 'worst' and a visual analogue scale of perception of spasticity (values from 0 to 10);

- performance in ADL was described in one study (Hugenholtz 1992) through an ad hoc prepared questionnaire where patients rated the effect of spasticity on ADL using a visual analogue scale from 0 to 5. Time of performing a dressing task (removing a pair of socks or slacks) was recorded;
- kinematic pattern of walking on a motor driven treadmill with bodyweight support was performed in one study (Stewart 1991).

b) Parallel study

The parallel trial comparing tizanidine with placebo (Nance 1994) included 118 patients, (104 male and 14 female), all had a SCI (traumatic etiology in 108 patients) at cervical and thoracic level. Most patients had a complete lesion. On the Frankel scale 66 patients were classified as A, 28 as B, and 23 as C. The age range was from 15 to 69 years. Mean duration of SCI was 95.2 months. The study did not describe whether participants were inpatients or outpatients.

Outcome was recorded at baseline (the day before randomisation, at the end of week 0), weekly during the titration phase, at the end of weeks five and seven during the plateau phase, and after completion of the tapering phase. The timing of assessment was standardised and set at one to two hours after delivery of the study medication.

The clinical outcomes used were:

- Ashworth scale (0 to 4) and video motion analysis of the pendulum test;
- spasm frequency during daytime and night-time awakenings (number of spasms recorded by patient via daily diary);
- muscle strength (score not described);
- ADL: modified Klein-Bell scale;
- global evaluation using separate visual analogue scale rated by the evaluators (minimal to normal 'functional and interactive capacity') and by the patients ('spasticity interferes/does not interfere with all/any function');
- adverse effects.

Risk of bias in included studies

In all the cross-over trials the treatment sequence was randomly assigned. The randomisation procedure was described in only one trial (Gruenthal 1997), where the pharmacist was in charge of assigning the treatment using a random number table without any contact with either patients or investigators. All trials were double-blind; see Characteristics of included studies for details. Duration of the cross-over trials ranged from three nights to eight weeks, so that in the longer study, even discounting the washout period, the duration of treatment might be a maximum of only four weeks.

Two trials (Burke 1971; Penn 1989) did not have a washout period between the two treatments. In the other six studies the washout period ranged from between 24 hours and two weeks.

In the Stewart trial (Stewart 1991) three male patients were lost to follow up due to illness or inability to comply with the protocol. In the Gruenthal trial (Gruenthal 1997) three men withdrew for unknown reasons, after receiving placebo as their initial treatment.

In the parallel trial (Nance 1994) the randomisation procedure was not reported, though titration of drugs and assessments were blinded. In this trial six patients did not receive the study medication after randomisation and were not described and considered in the analysis. Forty of the 118 participants (21 on tizanidine and 19 on placebo) were lost to follow up due to adverse effects (19 patients) or insufficient therapeutic effect (11 patients).

Effects of interventions

The poor quality of studies, and the marked differences in study designs, outcomes assessment and method of reporting, did not allow us to perform a quantitative combination (meta-analysis) of the results. We, therefore, report below a short summary of the main findings of each of the nine studies eligible for this review. Results are also summarised in table form.

Penn 1989
This study reported the effect of intrathecal baclofen infusion compared to saline placebo. After the baclofen intrathecal infusion period, the entire group of patients showed a mean reduction in the Ashworth score of 2.8 points, from 4.0 ± 1.0 to 1.2 ± 0.4 ($P < 0.0001$) and of 2.9 points in the spasm index from 3.3 ± 1.2 to 0.4 ± 0.8 ($P < 0.0005$). SCI patients were also examined separately and a significant reduction of the Ashworth and spasm scores ($P < 0.005$) is reported by the author graphically. Neurological examinations, motor control tests and patient self-assessment correctly identified the baclofen period in all patients. No adverse effects occurred. All patients were followed up in an open observational trial over an average of 19 months (range 10 to 33). In this second period, the Ashworth score and spasm score reduction observed in the cross-over trial were maintained at the first six months of follow-up. Complications that occurred during the open trial were dislodging of catheters (two patients) and pump failure (one patient). All problems were corrected with operations under local anaesthesia. No adverse effects were reported during this follow-up.

Hugenholtz 1992
This study also reported the effect of intrathecal baclofen infusion compared to saline placebo. Authors report a significant effect ($P < 0.05$) of baclofen intrathecal treatment on: reduction of lower limb tone and spasms (all six participants), improved questionnaire scores regarding ADL (five participants), improved passive range of movement (ROM) for lower limb joints (four participants). The effect was also regarded as clinically significant (according to the authors' criteria) in all these tests, except for passive ROM in the upper limb joints. The disability index, derived from the sum of the above tests, diminished considerably in all subjects during baclofen treatment. No numerical data are available for all the above mentioned outcomes, except for the overall number of patients who showed improvement.

All patients put on baclofen infusion were then followed in an open observational trial for an average of 30 days. As a group, participants maintained the baclofen effect observed during the cross-over period, with the exception of a loss of effect on lower limb reflexes and passive ROM of the upper limb joints. Disability index reduction during baclofen treatment was maintained in five patients. It is not clear when evaluations were carried out (whether in cross-over or open trial) for the timed dressing test and the scores for the Smith hand function evaluation test, but it was reported that they did not change appreciably. One participant experienced mild drowsiness following each of the first four doses of baclofen and two participants required initial repositioning of their lumbar catheter.

Kravitz 1992
This study could be considered as a sub-analysis of the Penn 1989 trial. Six patients, with an active pump already implanted from the Penn 1989 trial, were studied in order to evaluate the effect of baclofen infusion on electromyographic activity. Four of the six participants had a reduction in their phasic EMG activity while on baclofen. The baclofen effect did not reach significance at the P < 0.05 level. The reduction in EMG activity was statistically significant for EMG bursts occurring after arousal, but not before or without arousal. Results are expressed in graphical form.

Stewart 1991
This study compared the effect of clonidine to placebo. Five out of nine patients showed a reduction in the tonic stretch responses while on clonidine, while two out of nine showed no change or deterioration. Patients also showed a marked decrease in the visual analogue score, which was reported in the paper only as a graph. One paretic (Frankel C) patient demonstrated a functional walking improvement, becoming able to perform some steps with aids. No confidence intervals or statistical tests are reported in the text. Three patients were lost to follow up (all thoracic level, two Frankel A/B and one D; age 37, 45, 57 years; length from onset 2, 14, 20 years), because of illness or inability to comply with the protocol.

Gruenthal 1997
This study reported the effect of gabapentin compared to placebo. The effect of gabapentin resulted in an 11% reduction in the median Ashworth score (P = 0.044) and in a 20% reduction in the median score of the subjective perception of spasticity Likert scale (P = 0.0013), when compared to placebo. No difference was found in the other clinical measures. No confidence intervals for these reductions were reported in the text.

Corbett 1972
This study compared the effect of Valium, Amytal and placebo. Assessments were performed by six independent assessors (one was a patient) using a four-point scale ranging from 'worse' to 'much better'. The authors reported significant differences in favour of Valium versus placebo and also versus Amytal divided for the different assessors. When the assessment was made by the senior doctor and by the senior physiotherapist, $\chi^2 = 7.091$; P < 0.05 in 11 patients. Valium was also superior to Amytal when assessment was performed by a junior doctor and ward sister: $\chi^2 = 6.737$, P < 0.05 in 19 patients. The statistical analysis reported is not clear. Drowsiness was reported during different treatments by seven patients, six while on Valium, two on Amytal and three on placebo.

Burke 1971
This study compared the effects of baclofen with placebo in six patients previously treated with diazepam. After baclofen treatment, reduction of the spasticity scale was found in five out of six patients, three patients had less frequent spasms, and two had reduced duration of ankle clonus. No change was found in tendon reflexes. In all six patients, after treatment with baclofen, the stretch reflex diminished to a mean of 37.5% (0% to 67%) at a velocity of 200° per second. No formal statistical analysis was reported in the text.

Nance 1994
This study compared the effect of tizanidine versus placebo. Treatment in 40 patients out of the 124 randomised was discontinued prematurely due to adverse events (19 patients), insufficient therapeutic effect (11 patients) and for other causes not reported (10 patients). Six randomised patients did not receive tizanidine or placebo. These 46 patients were not included in the analysis. Tizanidine produced a significant (P < 0.0001) reduction in spasticity on the Ashworth score from baseline to end-titration (-3.70, SE 0.67), end-plateau (-4.35, SE 0.65), end-administration (-4.41, SE 0.57), compared to the placebo group. Video-motion analysis of the pendulum test showed significant improvement in tizanidine compared to placebo-treated patients at the end point (P < 0.04, median 14.56, SE 4.61). Only in the early treatment period could a significant reduction of the frequency of daytime spasms be observed.

No modification in muscle strength was registered in either group. No significant differences between the two groups were found in global evaluation of spasticity and functions (based on visual analogue scale) and in ADL assessment. In the tizanidine group, 81% of patients reported at least one adverse effect compared to 53% in the placebo group. The overall reporting rate of related adverse events was significantly different between the two groups (P = 0.002). The most commonly reported adverse effects in the tizanidine group were drowsiness, xerostomia (P < 0.001) and asthenia (not significant). No clinically meaningful differences were observed for vital signs or laboratory parameters.

DISCUSSION

It is widely accepted that patients with spinal cord injury should be treated according to a protocol where baclofen (with or without diazepam) represents the first step, followed (if needed) by other drugs such as dantrolene and, more recently, tizanidine. This review does not provide any supporting evidence for this commonly used therapeutic approach, as all available studies compare an active drug to placebo and there are no 'head-to-head' comparisons available. Moreover, only one trial included in this review (with six SCI patients) compared oral baclofen with placebo, while no comparison between intrathecal and oral baclofen nor any study assessing the effectiveness of dantrolene (against placebo or no treatment) is available. No better insight comes from cross-over follow up studies, in which there were very few patients. (In a total of eight cross-over studies looking at five different types of treatments, there were 100 patients, 86 of whom had SCI.)

The oral baclofen study included only six SCI patients, while the intrathecal study was based on a total of 14 (out of a total study population of 26 patients). This dissonance between research evidence and clinical practice is further underlined by the fact that the effectiveness of tizanidine, commonly seen at best as a second-line drug, is backed by the largest study (118 SCI patients).

A further important limitation of the studies included in this review stems from the heterogeneity of the outcome measures, as well as their limited clinical relevance regarding the need to assess the functional and subjective physical limitations suffered by patients.

Spasticity is characterised by a full range of clinical manifestations, all due to an increased stretch reflex, which affects the patient's autonomy and quality of life, as a result of problems in performing the activities of daily living, limitation of the range of motions, pain, and sleep disturbances. With this in mind, it is indeed a serious limitation in the studies that they looked almost exclusively at overall reduction in spasticity and in muscle spasms (measured through specific scales and/or electromyographic records), without paying attention to the influence of these treatments on the

patient's quality of life. No matter how difficult such measurements are to record, evidence-based clinical practice should be primarily based on patient-oriented outcome measures.

Even the relatively large positive study on tizanidine (limited in value due to the high number of dropouts as already discussed) documented an effect solely on spasms but failed to show a corresponding improvement in ADL and functional abilities, either when subjectively or objectively measured.

A further possible treatment is tetrahydrocannabinol, so far assessed in only a single case study with promising results (Maurer 1990). This trial compared delta-9 tetrahydrocannabinol (THC), codeine and placebo and was performed on a 38-year-old male with an incomplete paraplegia caused by a spinal ependymoma (Frankel C/D, level T1) complaining of marked spasticity, pain and leg paraesthesias. Outcomes were quality of sleep, pain, subjective spasticity, micturition, concentration and mood the day after taking medication and all were in favour of THC.

An issue that is currently under discussion with the Cochrane Multiple Sclerosis Group is whether it would be useful to produce a review that includes both spinal cord injury and multiple sclerosis patients. Given the high proportion of published articles that have a mixed population, we feel that discussion on this topic is needed. If it is concluded that there is justification for a review of the treatment of spasticity combining these two groups of patients, a joint review could be developed.

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide evidence for the care strategies presently used for patients with a spinal cord injury. There are some indications of an effect for baclofen and tizanidine against placebo on spasticity, but the outcome measures used are of limited clinical relevance. Moreover, the adverse effects of treatment are not negligible, especially tizanidine-associated drowsiness.

The justification of the current 'decision tree approach', which calls for the use of progressively more complex treatments guided by documented failures of previous steps, is extremely weak. Non-responders thus eventually become candidates for intrathecal baclofen (a demanding, expensive approach, that is not free of adverse effects) after previous failures with less invasive steps. The use of intrathecal baclofen should be restricted only to true non-responders, identified through a careful assessment of the extent of non-response.

Implications for research

Further research is urgently needed to ensure that patients with spinal cord injury receive evidence-based care. Further studies should include larger groups of patients and, most importantly, use more clinically relevant measures of treatment effects, including ADL and QoL measures administered at appropriate time intervals with respect to the realistic goals of patient recovery. The vast majority of currently available studies had too short a follow-up period to be able to assess clinically relevant end-points dealing with functional recovery. More 'head-to-head' comparison studies are needed, in order to get a full picture of the cost-benefits profile of the interventions, especially if a 'step-by-step' treatment strategy (from simpler to more complex protocols according to individual's clinical responses) is used.

Cross-over studies are, in our opinion, appropriate in this setting. Besides requiring smaller sample sizes, this approach makes patient recruitment easier without unduly jeopardising a patient's hopes that he/she will receive, sooner or later, an active treatment. Whatever the study design, assuring a sufficient follow-up period is crucial to increase the validity and clinical relevance of research in this area.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Burke 1971

Methods	Randomised double blind cross-over study. Randomisation procedure not described.
Participants	6 pts: 4 male, 2 female, all SCI (cervical level: 2 complete, 4 incomplete). Length from onset: not described. Age: 17 - 41 years. Inclusion criteria: SCI chronic pts (1 - 4 years). Exclusion criteria: Not described.
Interventions	2 periods of 14 days of baclofen or placebo, as tablets of identical appearance, without washout interval. Initial dose of 15 mg daily increasing by 15 mg every three days until 60 mg (five pts) and to 75 mg (one pt).
Outcomes	At baseline when patients were receiving diazepam (15 - 60 mg daily) daily: clinical assessments (a, b, c, d, e, f) after the first and second 14 days and EMG assessments (g). a) Spasticity (0 - 4); b) Muscle strength (0 - 5); c) Duration of ankle clonus (in seconds); d) Tendon reflexes (1 normal – 4 markedly increased); e) Number of spasms/day (recorded by the pts); f) Side-effects; g) EMG of the quadriceps muscle produced by passive flexion of the knee (at 200°/sec velocity).
Notes	No washout period. No functional outcomes.

Risk of bias

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

Corbett 1972

Methods	Randomised double blind cross-over study. Randomisation procedure not described.
Participants	22 pts: all traumatic SCI (15 tetraplegics and 7 paraplegics; 14 complete lesions and 8 incomplete lesions). Length from onset: 4 months. Age not reported. Inclusion criteria: Degree of spasticity varying from inconvenient to disabling. Exclusion criteria: Not described.
Interventions	Identical appearance tablets of placebo, Amytal 30 mg and Valium 5 mg during 3 periods of 2 weeks. Gradual increasing of doses from 1 to 3 tablets a day. 3 day of washout interval.
Outcomes	Observations made by six independent observers: daily by patient, senior doctor, senior physiotherapist, ward sister and once/twice a week by junior doctor and junior physiotherapist. Scores were expressed as: (-) worse, (0) no effect, (+) better and (++) much better.
Notes	Complete observations reported in 11 pts due to organisational problems.

Corbett 1972 *(Continued)*

	No clear criteria to assess spasticity variations.

Risk of bias

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

Gruenthal 1997

Methods	Randomised double blind cross-over trial. Randomisation by random number table performed by pharmacists blind to patients and assessors.
Participants	25 SCI pts: 22 male and 3 female (neurological level, completeness and autonomy not described), with spasticity due to SCI. Length from onset: 1 month - 26 years (median 7 years). Age: 21 - 60 years. Inclusion criteria: age above 18 years, spasticity due to SCI, not responsive to antispastic drugs. Exclusion criteria: pregnancy, history of renal disease, absence of spasms or rigidity.
Interventions	Placebo or gabapentin 400 mg x 3 daily for 48 hours, added to usual medications. 11 day washout interval.
Outcomes	Assessed at baseline (day 1), day 3, 15 and 17, at the same time and within 5 hours from the last drug administration. a) Subjective evaluation of spasm by Likert six-point scale; b) Ashworth scale (1 - 5); c) Muscle stretch reflexes (0 - 4); d) Clonus (0 - 3); e) Response to noxious stimuli (0 - 3).
Notes	Possible interference of concomitant antispastic treatment. No functional outcomes.

Risk of bias

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

Hugenholtz 1992

Methods	Randomised double blind cross-over study. Randomisation procedure not described.
Participants	6 pts: 2 MS, 4 SCI (cervical and thoracic level). Length from onset not reported. Age: 16 - 60 years. Independent on transfers at least by wheelchair. Inclusion criteria: SM and SCI only. Severe spasticity not controlled by oral antispastic drug and physiotherapy. Exclusion criteria: Systemic illness modifying spasticity. Prior ablative therapy on spinal cord, peripheral nerves or muscles. Prior tenotomies or joint fusions. Allergy to baclofen.
Interventions	Preliminary test with intrathecal baclofen (starting with 10 mg and increasing 5 - 10 mg doses until reduction of spasticity). All pts underwent the implantation of subcutaneous catheter access port (CAP) and optimum individual dose was determined. In a setting of 11 day cycle 2 individual therapeutic doses of Baclofen or saline placebo, by bolus injection at the same time of the day, on day 2 and 8 or 5 and 11. Washout interval of 48 hours.
Outcomes	At day 1, 2, 4, 5, 7, 8, 11. a) Questionnaire about effects of spasticity on daily activities (Visual Analogue Scale 0 - 5); b) Ashworth modified scale (0 - 5) at lower limb; c) Spasm score (0 - 4) at the trunk, upper and lower extremities; d) Reflex score (0 - 4) of biceps, triceps, patellar and achilles tendons); e) Passive ROM at hip, knee, ankle,

Hugenholtz 1992 *(Continued)*

	shoulder, elbow and wrist; f) Muscle strength scale (0 - 5); g) Timing of dressing task (removing a pair of socks or slacks); h) Smith Hand Function Evaluation; i) Urodynamic studies; j) Neurophysiological study (flexor reflex EMG of quadriceps, hamstring, gastrocnemius and anterior tibial muscles); k) Disability index made with sum of: questionnaire, passive ROM of lower limbs, spasm score for trunk and legs, motor tone and strength scores of the lower limbs.
Notes	

Risk of bias

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

Kravitz 1992

Methods	Randomised double blind cross-over study. Randomisation procedure not described.
Participants	6 pts: 2 MS and 4 SCI (3 cervical and 1 thoracic level). Length from onset not reported. Age: 29 - 45 years. Inclusion criteria: Pts self reporting sleep difficulty, selected from a group of 20 receiving the infusion device. Exclusion criteria: Not described.
Interventions	Intrathecal baclofen (doses ranged from 95.6 mg to 143.4 mg/day) or saline placebo infused in 2 non-consecutive nights. One day was considered a sufficient washout time.
Outcomes	Assessment performed in both study nights. a) Polysomnographic monitoring (electroencephalogram and submental EMG; b) EMG recordings at hamstrings, quadriceps, tibialis anterior, and gastrocnemius of the worse of the two legs; c) EMG Index (EMG event/hour of sleep). EMG events were grouped according to whether they occurred before, after or without arousals or awakenings.
Notes	No information on influence of quality of sleep on ADL or daytime quality of life.

Risk of bias

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

Nance 1994

Methods	Randomised, parallel-group, double blind, clinical trial. Randomisation procedure not described.
Participants	118 SCI pts, 104 male/14 female, 108 traumatic, cervical and thoracic level, Frankel: A (66 pts), B (28 pts), C (23 pts) Age: 15 - 69 baseline autonomy not specified. Mean length from onset: 95.2 months. Inclusion criteria: Spasticity secondary to SCI between C5 and T12, muscle tone at least 2 at Ashworth scale for at least one muscle group in the lower extremities, discontinuation of any drug likely to affect spasticity. Exclusion criteria: Severe hypertension, hypotension and contracture of the hip or knee.
Interventions	Phase 1: (week -1) washout period after discontinuing antispastic drugs; eligibility evaluation. Phase 2: (week 0) baseline phase: all eligible subjects received 1 week single-blind placebo treatment. Phase 3: (weeks 1 to 8) randomisation to placebo (40 patients) or tizanidine (38 patients), at dosage titrated from 4 to a maximum of 36 mg/d in 3 doses during the weeks 1 to 3 (titration phase). The individual

Nance 1994 *(Continued)*

	maximum doses reached at the end of titration were maintained during weeks 4 to 7 (plateau phase) and tapered to stop medication during week 8.
Outcomes	At baseline weekly during the titration phase, at the end of weeks 5 and 7 during the plateau phase, after completion of the tapering phase. Timing of examinations was standardised and performed 1 to 2 hours after the study medication was taken. a) Clinical outcomes: I. Muscle tone: Ashworth scale (0 - 4) and video motion analysis of the pendulum test; II. Spasm frequency during daytime and night-time awakenings; III. Muscle strength; b) ADL: modified Klein-Bell scale; c) Global evaluation: performed using separate visual analogue scale by the evaluator (minimal to normal "functional and interactive capacity") and by the pts ("spasticity interferes/does not interfere with all/any function"); d) adverse events.
Notes	40 patients interrupted the trial due to adverse events or insufficient therapeutic effect. Six pts, after randomisation, did not receive study medication and were not considered in the analysis.

Risk of bias

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

Penn 1989

Methods	Phase 1: Preliminary test with intrathecal baclofen (25, 50, 75 mg bolus doses). All pts underwent the pump implantation. Phase 2: Randomised double blind crossover study. Randomisation procedure not described. Phase 3: Open observational trial over an average of 19 months with 6 month intervals follow up.
Participants	20 pts: 10 MS, 10 SCI (cervical and thoracic level). Length from onset: average 2.2 years. Age: 23 - 62 years. All pts were dependent on ADL. 10 pts complained of pain and 9 of sleep disturbances. Inclusion criteria: Longstanding severe spasticity, severe disabling spasm not controlled by oral antispastic drug. Exclusion criteria: Not described.
Interventions	Baclofen or saline placebo (doses ranged from 62 mg to 749 mg daily; mean 340 mg daily) by continuing infusion for 3 day period. No washout interval.
Outcomes	At day 3 and 6. a) Ashworth scale (1 - 5) at hip, knee, ankle; b) Spasm frequency scale (0 - 4); c) EMG recordings: reflex H and M response, voluntary activity of legs; d) Neurological examination (tone, reflex, induced spasms, strength); e) Assessment by the pt of the "on" and "off" periods of baclofen.
Notes	No washout period. No functional outcome. No pts self reporting about ADL, pain and sleep disturbance.

Risk of bias

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

Stewart 1991

Methods	Randomised double blind cross-over study. Randomisation procedure not described.

Stewart 1991 *(Continued)*

Participants	12 pts: SCI (2 cervical and 10 thoracic level, 8 Frankel A/B, 1 C, 3 D). Length from onset: 1 - 20 years. Age: 19 - 57 years. Inclusion criteria: SCI chronic pts. Exclusion criteria: Not described.
Interventions	Tablets of identical appearance of clonidine or placebo 3 times a day, for 2 periods of 4 weeks. Initial doses 0.05 mg/day, increasing every 3 days until the optimal dose (0.10 mg - 0.50 mg/day) at the end of second week. 2 weeks of washout interval.
Outcomes	At base line and after 4 week medication period (in the morning after tablet). a) Kinematic pattern of walking on motor-driven treadmill with body weight support; b) EMG recordings (gluteus maximus, medial hamstrings, vastus lateralis, tibialis anterior, gastrocnemius); c) Ashworth scale (0 - 4) at ankle (with knee in extension and in flexion 90°) and knee; d) Visual analogue scale of subjective perception of spasticity (0 - 10); e) Ankle clonus (0 - 3). A change of at least 1 point (of outcome 3, 4, 5) was considered a significant improvement.
Notes	

Risk of bias

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

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

Study	Reason for exclusion
Ashby 1972	Less than 50% of patients were SCI.
Azouvi 1996	Observational study, no control group.
Basmajian 1973	Less than 50% of patients were SCI and results reported only as subjective evaluation by the author.
Basmajian 1974	Less than 50% of patients were SCI and results reported only as subjective evaluation by the author.
Bokonjic 1979	Less than 50% of patients were SCI.
Bovier 1985	No SCI patients included.
Broseta 1989	Observational study, no control group.
Chan 1994	Not a RCT.
Cocchiarella 1967	Less than 50% of SCI included.
Coffey 1993	Multicentre screening trial to select patients for pump implantation.
Cohan 1980	No SCI patients included.
Donovan 2000	Administration of treatment for 2 hours.
Fung 1990	Preliminary cross-over study on two subjects.

Study	Reason for exclusion
Glass 1974	Less than 50% of patients were SCI.
Growdon 1991	No SCI patients.
Harvey 1974	Less than 50% of patients were SCI.
Haslam 1974	No SCI patients included.
Hinderer 1990	Viscous and elastic stiffness of the ankle as the only outcome.
Hudgson 1971	Less than 50% of patients were SCI.
Hudgson 1972	Less than 50% of SCI patients.
Lee 1993	Less than 50% of patients were SCI.
Levine 1968	Only multiple sclerosis patients included.
Levine 1969	Only patients with multiple sclerosis.
Levine 1977	Less than 50% of patients were SCI.
Losin 1966	Only patients with cerebral palsy were included.
Lossius 1985	No SCI patients included.
Maurer 1990	Single case study.
Middel 1997	Less than 50% of SCI patients.
Monster 1973	Less than 50% of SCI patients.
Nance 1989	Vibratory inhibition of the H reflex as the only outcome.
Nance 1994a	Not a RCT.
O'Brien 1995	Only stroke patients included.
Ordia 1996	Less than 50% of SCI patients.
Pagano 1990	Less than 50% of patients were SCI.
Parke 1989	Observational study, no control group.
Pedersen 1970	Patients with non traumatic paraplegia (very likely due to MS).
Pirotte 1995	No control group.
Postma 1999	Not a RCT.
Priebe 1997	Only EMG outcome.
Richardson 2000	Less than 50% of patients SCI.
Roussan 1985	Less than 50% of patients SCI.

Study	Reason for exclusion
Schmidt 1976	Only multiple sclerosis patients included.
Segal 1999	Safety study where spasticity is a secondary outcome.
Wainberg 1990	Only treadmill and EMG outcome.
Weiser 1978	Less than 50% of SCI patients.
Wilson 1966	Less than 50% of SCI patients.

DATA AND ANALYSES

Comparison 1. Results of studies included in this review

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Available results for main outcomes			Other data	No numeric data

Analysis 1.1. Comparison 1 Results of studies included in this review, Outcome 1 Available results for main outcomes.

Available results for main outcomes

Study	
Burke 1971	No formal statistical analysis was reported in the text.
Corbett 1972	Graphically the effect of Valium was always superior to amytal or placebo. Statistical analysis not clearly reported.
Gruenthal 1997	11% reductions in the median Ashworth score (P=0.044), 20% reduction in the median score of the subjective perception of spasticity Likert scale (P=0.0013). No confidence intervals of these reduction are reported in the text.
Hugenholtz 1992	p<0.05 in reduction of lower limb tone and spasms, improved ADL, improved Range of Motion. No numerical data are available for these scales.
Kravitz 1992	Reduction in EMG activity was statistically significant for EMG bursts occurring after arousal.
Nance 1994	Tizanidine produced significant (P<0.0001) reduction in spasticity on the Ashworth score from baseline to end-administration (-4.41, SE 0.57), compared to placebo. Tizanidine showed improvements on the pendulum test at the end of treatment (P<0.04, median 14.56, SE 4.61). No modification in muscle strength was registered in either group. No significant difference was found in global evaluation of spasticity and functions and in ADL assessment. In the tizanidine group 81% of patients reported at least one adverse effect compared to 53% in the placebo group.
Penn 1989	Ashworth score: mean reduction of 2.8 points from 4.0 (SD 1.0) to 1.2 (SD 0.4) (P<0.0001) Spasm index: mean reduction of 2.9 points from 3.3 (SD 1.2) to 0.4 (SD 0.8) (P<0.0005).
Stewart 1991	Five out of nine patients showed a reduction in the tonic Stretch Responses while on clonidine. No confidence intervals or statistical tests are reported in the text.

APPENDICES

Appendix 1. Search strategies

Cochrane Injuries Group Specialised Register (searched 14 July 2008)
('spinal cord injur*' or SCI) AND (Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or Spastic* or spasms or intrathecal or antispas* or clonus)

CENTRAL (*The Cochrane Library* Issue 3, 2008)
1MeSH descriptor Spinal Cord Injuries explode all trees
#2 spinal cord near3 (injur* or damage* or contusion* or lacerat* or trauma*)
#3 (muscle* or muscular) near3 (spasm* or cramp* or spastic* or clonus)
#4 (#1 OR #2 OR #3)
#5 Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam
#6 antispas* or intrathecal
#7 (#5 OR #6)
#8 (#4 AND #7)

MEDLINE (1950 to July (week 1) 2008)
(Also PubMed-searched)
1.exp Spinal Cord Injuries/
2.(spinal cord adj3 (injur* or damage* or contusion* or lacerat* or trauma*)).ab,ti.
3.((muscle* or muscular) adj3 (spasm* or cramp* or spastic* or clonus)).ab,ti.
4.1 or 2 or 3
5.exp Baclofen/
6.exp Dantrolene/
7.exp Clonidine/
8.exp Diazepam/
9.(antispas* or intrathecal).ab,ti.
10.(Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam).ab,ti.
11.5 or 6 or 7 or 8 or 9 or 10
12.4 and 11
13.randomi?ed.ab.
14.randomized controlled trial.pt.
15.controlled clinical trial.pt.
16.placebo.ab.
17.clinical trials as topic.sh.
18.randomly.ab.
19.trial.ti.
20.or/13-19
21.humans.sh.
22.20 and 21
23.12 and 22

PubMed (searched 15 July 2008 [last 5 years])
1.exp Spinal Cord Injuries/
2.(spinal cord AND (injur* or damage* or contusion* or lacerat* or trauma*)).ab,ti.
3.((muscle* or muscular) AND (spasm* or cramp* or spastic* or clonus)).ab,ti.
4.1 or 2 or 3
5.antispas* or intrathecal
6.Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam

7.5 or 6
8.4 and 7
9.(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh]) NOT ((models, animal[mh] OR Animals[mh] OR Animal Experimentation[mh] OR Disease Models, Animal[mh] OR Animals, Laboratory[mh]) NOT (Humans[mh]))
10.8 and 9

EMBASE (1980 to July 2008)
1.exp Spinal Cord Injury/
2.(spinal cord adj3 (injur* or damage* or contusion* or lacerat* or trauma*)).ab,ti.
3.((muscle* or muscular) adj3 (spasm* or cramp* or spastic* or clonus)).ab,ti.
4.1 or 2 or 3
5.exp Baclofen/
6.exp Dantrolene/
7.Clonidine/
8.Diazepam/
9.(antispas* or intrathecal).ab,ti.
10.(Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam).ab,ti.
11.5 or 6 or 7 or 8 or 9 or 10
12.4 and 11
13.exp Randomized Controlled Trial/
14.exp controlled clinical trial/
15.randomi?ed.ab.
16.placebo.ab.
17.exp Clinical Trial/
18.randomly.ab.
19.trial.ti.
20.13 or 14 or 15 or 16 or 17 or 18 or 19
21.exp human/
22.20 and 21
23.12 and 22

Current Controlled Trials Meta Register of controlled trials
[http://www.controlled-trials.com/mrct/] (searched 15 July 2008)
Spinal cord and spasticity

CINAHL (1982 to 2008)
1.MH Spinal Cord Injuries/
2.TX "spinal cord" and TX (injur* or damage* or contusion* or lacerat* or trauma*)
3.TX (muscle* or muscular) and TX (spasm* or cramp* or spastic* or clonus)
4.S1 or S2 or S3
5.AB (antispas* or intrathecal) or TI (antispas* or intrathecal)
6.AB (Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam) or TI (Dantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam)
7.S5 or S6
8.(MH "Random Assignment")
9.(MH "Clinical Trials")
10.(MH "Experimental Studies")
11.(MH "Double-Blind Studies")
12.(MH "Single-Blind Studies")
13.(MH "Triple-Blind Studies")
14.AB random* or TI (random* or trial*) or AB placebo*
15.S8 or S9 or S10 or S11 or S12 or S13 or S14
16.S4 and S7 and S15

Web of Science (1970 to 2008) (searched 15 July 2008)
1.Topic=(spinal cord) AND Topic=(injur* or damage* or contusion* or lacerat* or trauma*) AND Topic=(antispas* or intrathecalDantrolen* or Dantrium or Diazepam or Valium or Novodipam or Relanium or Seduxen or Diazepam* or Valrelease or Diapam or Stesolid or Anxicalm or Valpam or Vival or Normabel or Bensedin or Stedon or Plidex or Betapam or Dipaz or Tizanidine or Zanaflex or Mionidin or Sirdalud or Clonidine or Catapres or Clorpres or Duraclon or Baclofen or Lioresal or Kemstro or baclofen* or dantrolene or tizanidine or clonidine or diazepam)
2.Topic=(placebo or randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials)
3.1 AND 2

ZETOC (searched 16 July 2004 to 2008)
Spinal, cord, spasticity.

WHAT'S NEW

Date	Event	Description
23 June 2009	New search has been performed	The search has been updated to July 2008. No new studies for inclusion were identified. The results and conclusions remain the same.

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 2000

Date	Event	Description
11 July 2008	Amended	Converted to new review format.
18 August 2004	New search has been performed	The search was updated in August 2004, no new studies for inclusion were identified. The discussion has been amended in light of the addition of a number of excluded studies.

CONTRIBUTIONS OF AUTHORS

Mariangela Taricco and Roberto Adone screened citations for eligibility, extracted data and wrote up the review.
Cristina Pagliacci and Elena Telaro screened citations for eligibility, extracted data and helped to write and revise the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Intramural, Italy.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Baclofen [therapeutic use]; Clonidine [analogs & derivatives] [therapeutic use]; Dantrolene [therapeutic use]; Muscle Relaxants, Central [*therapeutic use]; Parasympatholytics [*therapeutic use]; Spasm [*drug therapy] [*etiology]; Spinal Cord Injuries [*complications]

MeSH check words

Humans