

Treatments for spasticity and pain in multiple sclerosis: a systematic review

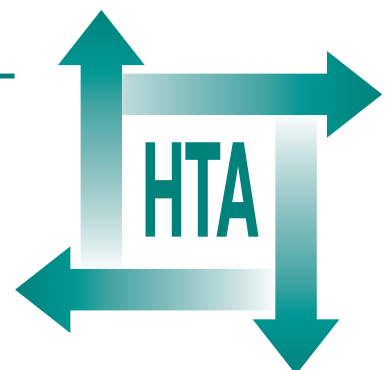
S Beard

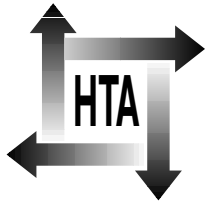
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Treatments for spasticity and pain in multiple sclerosis: a systematic review

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Abstract

Treatments for spasticity and pain in multiple sclerosis: a systematic review

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Objectives: To identify the drug treatments currently available for the management of spasticity and pain in multiple sclerosis (MS), and to evaluate their clinical and cost-effectiveness.

Data sources: Electronic bibliographic databases, National Research Register, MRC Clinical Trials Register and the US National Institutes of Health Clinical Trials Register.

Review methods: Systematic searches identified 15 interventions for the treatment of spasticity and 15 interventions for treatment of pain. The quality and outcomes of the studies were evaluated. Reviews of the treatment of spasticity and pain when due to other aetiologies were also sought.

Results: There is limited evidence of the effectiveness of four oral drugs for spasticity: baclofen, dantrolene, diazepam and tizanidine. Tizanidine appears to be no more effective than comparator drugs such as baclofen and has a slightly different side-effects profile. Despite claims that it causes less muscle weakness, there was very little evidence that tizanidine performed any better in this respect than other drugs, although it is more expensive. The findings of this review are consistent with reviews of the same treatments for spasticity derived from other aetiologies. There is good evidence that both botulinum toxin (BT) and intrathecal baclofen are effective in reducing spasticity, and both are associated with functional benefit. However, they are invasive, and substantially more expensive. None of the studies included in the review of pain were

designed specifically to evaluate the alleviation of pain in patients with MS and there was no consistency regarding the use of validated outcome measures. It was suggested that, although expensive, the use of intrathecal baclofen may be associated with significant savings in hospitalisation costs in relation to bed-bound patients who are at risk of developing pressure sores, thus enhancing its cost-effectiveness. No studies of cost-effectiveness were identified in the review of pain. There is evidence, albeit limited, of the clinical effectiveness of baclofen, dantrolene, diazepam, tizanidine, intrathecal baclofen and BT and of the potential cost-effectiveness of intrathecal baclofen in the treatment of spasticity in MS.

Conclusions: Many of the interventions identified are not licensed for the alleviation of pain or spasticity in MS and the lack of evidence relating to their effectiveness may also limit their widespread use. Indeed, forthcoming information relating to the use of cannabinoids in MS may result in there being better evidence of the effectiveness of new treatments than of any of the currently used drugs. It may therefore be of value to carry out double-blind randomised controlled trials of interventions used in current practice, where outcomes could include functional benefit and impact on quality of life. Further research into the development and validation of outcomes measures for pain and spasticity may also be useful, as perhaps would cost-utility studies.





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List of abbreviations

ACTH	adrenocorticotrophic	MHI	Mental Health Inventory
ADL	activities of daily living	MRC	Medical Research Council
AMB	ambulation index	MS	multiple sclerosis
BT	botulinum toxin	MSIS	MS Impairment Scale
CCS	chronic cerebellar stimulation	NICE	National Institute for Clinical Excellence
CIBI	continuous intrathecal baclofen infusion	NRS	Neurologic Rating Scale
CNS	central nervous system	NSAID	non-steroidal anti-inflammatory drug
CSF	cerebrospinal fluid	QoL	quality of life
DSS	Disability Status Scale	RCT	randomised controlled trial
DB	double blind	SCI	spinal cord injury
DREZ	dorsal root entry zone	SF-36	Short Form with 36 Items
EDSS	Expanded Disability Status Scale	SIP	Sickness Impact Profile
EMG	electromyographic	TAA	turn/amplitude analysis
GABA	γ -aminobutyric acid	TENS	transcutaneous electrical nerve stimulation
IHQL	Index of Health Related Quality of Life	TGN	trigeminal neuralgia

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

Multiple sclerosis (MS) is one of the commonest neurological conditions of young adults in the Western world, with an estimated 58,000–63,000 people with the disease in England and Wales. Pain and spasticity are two of the commonest symptoms from which people with MS suffer. A recent survey of members by the MS Society found that 54% reported pain as a current symptom and 74% spasticity. The importance of these symptoms is not simply because of their frequency, but also because of the impact they have on daily life. As the disease progresses, so does the spasticity, resulting in muscle spasms, immobility, disturbed sleep and pain. Disability resulting from spasticity can lead to patients requiring extensive nursing care.

Pain can be caused by a variety of factors including spasticity itself, in addition to neuronal damage due to the disease process. Not uncommonly, it may be musculoskeletal in origin, arising as a result of abnormal posture following the disability caused by MS.

Methods

A systematic review was undertaken to identify what treatments are available for the management of pain and spasticity in MS and to evaluate clinical and cost effectiveness through assessment of the best available evidence. The scope of the review was limited to the consideration of drug treatments. It did not include non-drug therapy or surgical treatments. It did not consider cannabinoids, clinical trials of which were ongoing at the time of the review. Reviews of the treatment of spasticity and pain when due to other aetiologies were also sought and their conclusions were examined for consistency with the conclusions in the primary studies identified.

Results

Spasticity

Systematic searches for evidence relating to the treatment of spasticity identified 15 interventions for inclusion:

- baclofen (Lioresal)
- dantrolene (Dantrium)
- tizanidine (Zanaflex)
- diazepam
- gabapentin (Neurontin)
- botulinum toxin (BT) (Botox, Dysport)
- intrathecal baclofen (Lioresal Intrathecal)
- phenol
- threonine
- vigabatrin
- clonidine
- methylprednisone
- cyproheptadine
- magnesium
- ketazolam.

Sixty-seven papers, 41 of which were described as double-blind randomised controlled trials (RCTs), were included in the review of spasticity. Overall, the quality of the studies was poor. A wide variety of outcome measures were used. In cases where the same outcome measures were used, there were inconsistencies in the application of instruments and analysis of results across studies.

There is limited evidence of the effectiveness of four oral drugs for spasticity: baclofen, dantrolene, diazepam and tizanidine. All appear to be approximately equally effective at reducing spasticity when assessed clinically, although in no case is there any good evidence of functional benefit. Tizanidine appears to be no more effective than comparator drugs such as baclofen. Tizanidine has a slightly different side-effects profile in that the main side-effect of tizadine is a dry mouth. Despite claims that it causes less muscle weakness, there was very little evidence that tizanidine performed any better in this respect than other drugs, although it is more expensive. The findings of this review are consistent with reviews of the same treatments for spasticity derived from other aetiologies.

There is no good evidence of effectiveness for gapapentin, threonine, vigabatrin, methylprednisolone, cyprohepladine or magnesium.

There is good evidence that both BT and intrathecal baclofen are effective in reducing

spasticity, and both are associated with functional benefit. However, they are invasive, and substantially more expensive. Their use is most appropriately restricted to people with severe disabling spasticity.

Pain

Systematic searches for evidence relating to the treatment of pain identified 15 interventions:

- carbamazepine
- phenytoin
- gabapentin
- lamotrigine
- tricyclic antidepressants
- steroids
- baclofen
- intrathecal baclofen
- amantadine
- misoprostol
- octreotide
- bupivacaine
- acetazolamide
- lidocaine
- mexiletine.

Thirty-three studies were included in the review of pain. None of the studies were RCTs designed specifically to evaluate the alleviation of pain in patients with MS. The majority of papers were non-systematic reviews, small case series or individual case reports. There was no consistency regarding the use of validated outcome measures. Most papers recorded only that pain had or had not been relieved.

Cost-effectiveness and clinical effectiveness

In the absence of formal research of any quality in this area, it is not possible to draw conclusions regarding the effectiveness or otherwise of the interventions identified.

Evidence relating to the cost-effectiveness of treatments was extremely limited. In the review of spasticity, five health economic evaluations of intrathecal baclofen were identified. No studies relating to the remaining treatments were identified. The five studies suggested that

although expensive, the use of intrathecal baclofen may be associated with significant savings in hospitalisation costs in relation to bed-bound patients who are at risk of developing pressure sores, thus enhancing its cost-effectiveness. No studies of cost-effectiveness were identified in the review of pain.

There is evidence, albeit limited, of the clinical effectiveness of baclofen, dantrolene, diazepam, tizanidine, intrathecal baclofen and BT and of the potential cost-effectiveness of intrathecal baclofen in the treatment of spasticity in MS. Owing to the paucity and poor quality of evidence identified in this review, no further conclusions regarding the clinical or cost-effectiveness of the remaining interventions for pain or spasticity can be drawn.

Conclusions

Many of the interventions identified are not licensed for the alleviation of pain or spasticity in MS. In addition, the lack of evidence relating to their effectiveness may militate against them being used consistently across the NHS. Lastly, the licensing and forthcoming availability of trial evidence relating to the use of cannabinoids in the alleviation of symptoms relating to MS may mean that we are in the ironic position of having better evidence of the effectiveness of new treatments than of any of the currently used drugs.

Recommendations for research

The following areas are suggested for further research:

- Double-blind RCTs, with adequate power and follow-up, of interventions used in current practice for the alleviation of pain and spasticity in MS. Outcomes should include functional benefit and impact on quality of life.
- Development and validation of outcomes measures for pain and spasticity.
- Cost-utility studies.

Chapter I

Aim and background

Aim of the report

This report addresses two questions:

- What are the treatments currently available for the management of spasticity and pain in multiple sclerosis (MS)?
- What is the clinical and cost-effectiveness of each of these treatments for spasticity and pain in MS?

The purpose of this report is to provide a wider perspective of the needs and potential interventions in MS. It is not possible to cover each individual treatment in great depth. Treatments other than drug therapy are not within the remit of this report.

Background

The treatment of MS has been identified by the National Institute for Clinical Excellence (NICE) as an important area for evaluation. There is no cure, and treatments currently available are directed towards slowing the progression of disease, reducing relapses or alleviating the wide spectrum of symptoms. This report is part of a series evaluating the effectiveness and cost-effectiveness of interventions for MS.

MS is an inflammatory disease, which results in myelin loss in the central nervous system (CNS). This in turn leads to the development of sclerotic patches known as plaques in the brain and spinal cord. Although the aetiology is unknown, there is strong evidence that MS is the result of an autoimmune response.

Epidemiology

MS is one of the most common neurological conditions affecting young adults in the Western world. The prevalence of MS in England and Wales is around 110–120 per 100,000, although this varies geographically, with a higher prevalence in the north of England.¹ This translates to between 58,000 and 63,000 cases for England and Wales, although some estimates have been higher.

MS is twice as common in women than men. There is evidence that patients with MS are starting to live longer¹ and this will have implications for the number of patients experiencing severe spasticity.

Symptoms

The progression of the disease is extremely variable. While initially the disease may be relapsing and remitting, it usually becomes progressive over time, resulting in chronic disability. The signs and symptoms of MS are variable, but generally reflect the degree of demyelination that has taken place. The main presenting symptoms of MS are:²

- weakness in one or more limbs
- optic neuritis
- paraesthesiae
- diplopia
- vertigo
- disturbance of micturition.

As the disease progresses, other symptoms become more significant. A recent survey by the MS Society of 275 members (all patients with established MS) reported fatigue, spasticity (stiffness, spasms or both) and problems with balance as the most commonly experienced symptoms (233 responses received – a rate of 80%).³ Results are summarised in *Table 1*.

Recently, attention has focused on new drugs for slowing disease progression and reducing relapses. However, the identification of effective drugs for the alleviation of symptoms remains very important. Spasticity and pain are two of the most important symptoms experienced by sufferers of MS, both because of their frequency, but also because of the impact on daily life. As the disease progresses, so does the spasticity, resulting in muscle spasms, immobility, disturbed sleep and pain. Disability resulting from spasticity can lead to patients requiring extensive nursing care.

Pain can be caused by a variety of factors, including spasticity itself, in addition to neuronal damage. Not uncommonly it may be musculoskeletal in

TABLE 1 Results of the MS Society survey

Symptom	% currently experiencing symptom (top 8)	% rating symptom as one of three worst (top 8)
Fatigue	86	65
Bladder or bowel problems	66	50
Balance problems	73	44
Muscle weakness	69	44
Visual problems	Not available	20
Pain	54	18
Muscle stiffness	64	17
Muscle spasms	51	14
Spasticity (stiffness or spasm or both)	74	Not available
Numbness/tingling	64	Not available

origin, arising as a result of abnormal posture following the disability caused by MS.

Structure of this report

This report contains two separate reviews: one of the effectiveness and cost-effectiveness of treatment for spasticity in MS and the other of treatment for pain. In each case, the problem is described, followed by what is known of current

treatment, then the methods and findings of the review are reported. A review, limited by the amount of available evidence, of the economic aspects of the treatment of spasticity is included. There is no economic review of the treatment of pain, as no literature was identified relating to this. Overall, there was substantially more primary literature identified dealing with the treatment of spasticity than of pain, and this is reflected in the relative length and in the structure of reporting of the two reviews.

Chapter 2

Spasticity in MS

Nature and aetiology of spasticity in MS

Spasticity, or increased tone, is a motor disorder caused by lesions of the CNS involving the upper motor neurones. It is associated with sprouting of descending motor pathways to form new synaptic connections with spinal neurones and with denervation hypersensitivity. It is more common in the lower limbs.

Spasticity is a major contributor to disability in MS. It can cause pain, inability to walk and, later, problems with personal hygiene. Indeed, it is spasticity rather than weakness in the limbs which accounts for much of the disability affecting lower limbs.

The severity of spasticity increases as the disease progresses. Initially increased tone may be manifest as extensor spasms. These are particularly likely to occur at night or on waking in the morning. They may be so severe as to eject the patient from a wheelchair. The legs are held rigidly extended for several minutes.

However, as the disease progresses, the spasticity begins to affect the flexor tone, which initially results in the patient falling over unexpectedly. In contrast to sudden extension, flexor spasms are frequently painful. Over time, the flexed posture can become more frequent and eventually permanent. The increased muscle tone eventually leads to difficulties in nursing care and in maintaining hygiene. In some cases this can lead to bed sores, which in turn exacerbate the muscle spasms. It is important to bear in mind that spasticity can be a useful function in the earlier stages of the disease, particularly whilst the patient is still ambulatory, and may assist the patient in standing. However, the need to treat spasticity increases as the disease progresses. In non-ambulatory patients the spasticity can become painful and problematic, making transfer of the patient difficult and causing problems for the carers of patients, particularly in maintaining hygiene.

Epidemiology of spasticity in MS

Spasticity has been estimated to affect between 40 and 60% of all patients with MS. In the MS Society survey undertaken in October 1997,³ 64% of respondents reported muscle stiffness and 51% muscle spasms. Overall, 74% reported stiffness, spasms or both. However, although the response rate of 80% was high, it is likely that both the less, in addition to the more, disabled patients were excluded. Nevertheless, it does give an indication as to the scale of the problem.

Impact and prognosis of spasticity in MS

It is difficult to be precise about the prognosis of MS since the evidence is poor. Surveys indicate that approximately 50% of patients with MS are independent and still able to walk after 15 years. A review of survival studies by Compston and Swinglar indicates that some 75% of patients survive for 25 years.⁴ Nevertheless, severe spasticity can result in complete immobility. It is not known how many MS patients enter the helpless bedridden stage.²

Although the authors were not able to identify any peer-reviewed literature concerning the impact of spasticity on the quality of life (QoL) of patients with MS, a poster presented at an MS Society conference⁵ reported on the Short Form with 36 Items (SF-36) scores of 174 people with spasticity related to MS. This suggested a clear reduction, with increasing spasticity, in SF-36 scores in all except the 'role physical' dimension. Interestingly, in this sample, 41% of respondents claimed never to have seen a neurologist, 56% never to have seen a specialist in a rehabilitation centre and 60% never to have seen an MS or neurology specialist nurse.

Current service provision

It was not possible to identify any formal review of current clinical practice regarding the treatment of spasticity in MS. Anecdotal reports suggest that it

may be very variable. The MS Society survey referred to above reported that 32% of patients did not see a hospital specialist for treatment.³ Reasons varied from patient unhappiness with previous experience of hospital specialists to general practitioners (GPs) telling them 'that nothing can be done for MS'. The survey also found that overall 37% of patients had taken baclofen, 9% diazepam and 2% dantrolene in the previous 2 years. No information was available for any other antispastic drugs. Of those who had taken baclofen, 42% had had side-effects, most commonly weakness.

Current clinical reviews of treatment suggest that the standard treatment for moderate spasticity is oral therapy including baclofen, dantrolene, diazepam and, more recently, tizanidine. Sometimes, combinations of these therapies are used. Pharmacological interventions are usually supported by physiotherapy; however, the effectiveness of physiotherapy has not been assessed in this review. MS requires a multi-disciplinary team approach bringing together neurologists, physiotherapy and nursing care. Physiotherapy in particular is used to develop a programme of stretching and range-of-motion exercises.

It has been suggested that some GPs may be reluctant to prescribe the more expensive antispastic drugs (e.g. tizanidine), though no evidence has been put forward to substantiate this. The average daily cost of tizanidine is more than twice that of baclofen. Access to more invasive treatment, in particular, continuous intrathecal baclofen infusion (CIBI), appears to be extremely variable and depends on the availability of the service and local clinical practice. Again, there does not appear to be any systematic information

on this. The use of CIBI appears to be low; for instance, in 1998 in the whole of Britain, around 200 patients were implanted with a pump for intrathecal baclofen, of whom only around 60 had MS.⁶ This is likely also to be true of the intramuscular botulinum toxin (BT) injection, which it should be noted is not licensed for this indication.

Criteria for treatment

When considering treatments for spasticity, it is important to recognise that the desired effect may change over time as the disease progresses. It is necessary to distinguish between the less severe spasticity in the early stages of MS when the patient will still be ambulant and more severe spasticity in the advanced stages of MS when the patient may be non-ambulant.

Treatment for spasticity aimed at reducing muscle tone may achieve this at the expense of increased weakness. This, in turn, can lead to no improvement in function or even a deterioration of function. Spasticity itself can be helpful to an ambulant patient and treatment is only necessary when the spasticity becomes a problem.

In the early stages of the disease, patients who are still ambulant will usually receive oral drugs. However, in non-ambulant patients, there may be greater emphasis on increasing comfort and facilitating nursing care even if this results in greater muscle weakness and less mobility. Injectable or intrathecal drugs are more likely to be given to non-ambulant patients. Once a patient becomes unresponsive to oral therapy, then the choices are limited to CIBI or intramuscular injections of BT.

Chapter 3

Review of treatments for spasticity: methods

Formal scoping review

The aim of the search was to identify treatments for inclusion in the review, and to locate relevant randomised controlled trials (RCTs), reviews and cost-effectiveness studies.

Initial scoping searches were conducted to identify references relating to MS and spasticity. The main aims of the initial searches were twofold: to identify interventions to contribute to the framework of treatments considered in the review; and to identify search terms to inform the development of further, comprehensive search strategies. Therefore, search strategies at this stage were designed to optimise the specificity of the search results. The searches were undertaken in January 2000 on MEDLINE, EMBASE and the Science Citation Index. Search results were not limited by date, language or by study or publication type.

Comprehensive search strategies were then constructed to identify papers relating to MS and the individual treatments for spasticity. Search results were not restricted by date, but were restricted to English language. Filters to limit search results to RCTs, reviews or cost-effectiveness studies were applied. Searches were undertaken in June and July 2000 on the following databases:

- MEDLINE
- EMBASE
- Science Citation Index
- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL/CCTR (Cochrane Controlled Trials Register)
- PubMed
- HealthSTAR
- Best Evidence
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- AMED (Allied and Complementary Medicine)
- NHS CRD DARE (Database of Abstracts of Reviews of Effectiveness)
- NHS CRD NHS EED (NHS Economic Evaluation Database)

- NHS CRD HTA (Health Technology Assessment).

Search strategies for MEDLINE are given in Appendix 3. Search strategies for other databases are available from the authors.

In addition to searches of electronic bibliographic databases, sources were consulted to identify studies not retrieved through database searching, current research and grey literature. The National Research Register (NRR), MRC Clinical Trials Register and the US National Institutes of Health (NIH) Clinical Trials Register were searched. The publication lists and current research registers of health technology assessment and guideline-producing agencies and funding and regulatory bodies were consulted. Searches were repeated in March 2002.

Inclusion criteria

In selecting studies to be included in this review, the following criteria were used:

- at least 50% of the trial subjects had to be diagnosed as having MS or
- if less than 50% of subjects had MS, then the findings for the MS patients had to be presented separately.

The inclusion criteria regarding study design were based on 'best available' evidence. Where possible, the review was restricted to RCTs. However, this was not always possible owing to lack of RCT evidence in which case studies of weaker design were included. Details are given in individual chapters.

Quality assessment strategy

The Jadad scale was used for assessing the quality of the papers selected for inclusion in this review.⁷ Details are given in Appendix 1.

Methods of analysis and synthesis

The data were analysed by drug and summarised in a tabular format. Validity of outcome measures, validity of design and statistical analysis were

specifically considered. Direction of effect was summarised. It was not possible to carry out a meta-analysis of the findings since there was a wide variety of outcome measures employed and, even where the same outcome measure was employed, it was often in incompatible forms.

Chapter 4

Results of the systematic review of treatments for spasticity in MS

Description of the interventions considered

This review considers drug treatments for spasticity and does not include non-drug therapy or surgical treatments. The drug treatments which are considered are:

- baclofen (Lioresal)
- dantrolene (Dantrium)
- tizanidine (Zanaflex)
- diazepam
- gabapentin (Neurontin)
- botulinum toxin (Botox, Dysport)
- intrathecal baclofen (Lioresal Intrathecal)
- phenol
- threonine
- vigabatrin
- clonidine
- methylprednisone
- cyproheptadine
- magnesium
- ketazolam.

This review excludes cannabinoids, although anecdotal evidence suggests they may be effective at treating both spasticity and pain. Clinical trials are in progress to evaluate their role.

Existing reviews

In addition to this review, two published systematic reviews relating to drug treatment for spasticity were identified. A Cochrane review, last updated in June 2001, identified 23 placebo-controlled trials on antispasticity agents for MS⁸ and Creedon and colleagues carried out a meta-analysis of intrathecal baclofen in 1997.⁹ This took the form of a meta-analysis of English language trials of published studies on intrathecal baclofen prior to June 1996 and covered 27 studies including 162 patients with MS. There were also various reviews of single antispasticity agents in non-MS conditions which have been referred to in the discussion.

Oral baclofen (Lioresal)

Baclofen is a γ -aminobutyric acid (GABA) derivative which, unlike the parent compound, crosses the blood-brain barrier, albeit to a limited extent. GABA is a major inhibitor of impulse transmission in the nervous system, and baclofen is thought to exert an antispastic effect through inhibiting reflex neurological transmissions in the spinal cord via its effect on GABA receptors. The cost of baclofen is £10.84 for 84 5-mg tablets.¹⁰ The maximum daily dose is 100 mg. At this dosage, the average daily cost of oral baclofen would be £2.58.

Quantity of research available

The search strategy identified 16 papers. Four of these were excluded, two because they did not include patients with MS, one because, although it did include MS patients, they were fewer than half of all the patients and results were not shown separately, and one because it was a second publication of the same study with a different lead author.

Eleven randomised and one non-randomised double-blind (DB) controlled trials of the effect of baclofen on spasticity were identified. Nine (including the non-randomised study) were comparisons with placebo, three with diazepam. One of the latter also reported comparison with placebo. In this one, the evaluating physician would not have been blind to the placebo comparison (and it is not altogether clear that the patients would have been either). One of these studies also involved assessing the effect of the drug on muscle strength, and this was reported separately. Nine were crossover studies, two parallel group studies, and in one it was not clear. Study details are summarised in *Tables 2 and 3*.

Populations examined

Seven of the studies recruited exclusively patients with MS, described variously as 'established' or 'clinically definite'. In the others the majority of patients had MS. The age range where stated was

TABLE 2 Baclofen vs placebo

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Jerusalem (1968), Germany ¹⁹	DB parallel group RCT, single centre	Baclofen 16 patients, placebo 14. Baclofen titrated up to 80 mg/day. Duration not explicit (>8 days). All had exercise and hydrotherapy	N = 30. 29 with MS, one with syringomyelia. Non-progressive for 6 months. Majority housebound, none bedridden	None	Four grades of success identified (none, slight, good, very good) according to change on an <i>ad hoc</i> five-point scale	Success reported in 12/16 patients on baclofen, 5/14 on placebo. Difference reported to be 'statistically significant'. Night spasms helped in 8/9 patients. Of 25 patients in total who took baclofen (including patients transferred from placebo), 7 reported sedation, 5 weakness (leading to reduction in dose), 1 nausea, 1 dry mouth	3/5
Hudgson <i>et al.</i> (1971), UK ^{14,20}	DB crossover RCT, single centre	Baclofen 30 mg/day for 10 days, placebo 7 days, washout	N = 23. 18 with MS. Aged 30–63 y. 16 M, 7 F. All had spasticity graded at 3–4/4 on the Ashworth scale	None	Assessment of spasticity using Ashworth scale, at the start and finish of baclofen and placebo treatment. Subjective assessment	Degree of improvement in spasticity greater on baclofen than placebo in 16 patients, greater on placebo than baclofen in 7 patients. Mean change in score was 1.44 on baclofen, 0.54 on placebo ($p < 0.05$). 13 patients said stiffness reduced on baclofen, 5 on placebo, 5 reported no difference. Side-effects (mild nausea) in 6 patients on baclofen, 3 on placebo	4/5

continued

TABLE 2 Baclofen vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Basmajian (1975), USA ²¹	DB crossover RCT, single centre	Baclofen (dose not specified) for 4 weeks, placebo for 4 weeks, 1 week washout	N = 14. All with MS. Aged 21–55 y. MS with spasticity for >3 months	N = 3, 'for personal reasons unrelated to therapy'	Not stated	Baclofen superior in 7/11 patients, placebo superior in 3/11. When 8 additional patients from an earlier study are included, baclofen was superior in a total of 9/19, placebo superior in 5/19, and neither drug superior in 5/19. No information on-side effects	4/5
Levine et al. (1977), USA ¹⁶	DB controlled trial, possibly crossover (does not appear to have been randomised)	Baclofen increasing 15–80 mg/day on predetermined schedule. Placebo. Treatment for 5 weeks, washout for 3 weeks	N = 19. Average age 43 y. 5 F, 12 M. 12 had MS. Patients were all severely disabled, confined either to bed or wheelchair	N = 1; however, all patients did not complete all tests	Muscle hypertonicity using EMG. Measurements of change in MSV (microvolt seconds) before and after the test drug. Clinical grading score (CLN)	53% drop in MSV on baclofen, 5% on placebo. 82% of MS patients had >30% fall in MVS on baclofen, compared with 21% on placebo. No statistical analysis. No difference to placebo, but analysis is unclear. Baclofen was well tolerated and any side-effects seem to be dose related	2/5

continued

TABLE 2 Baclofen vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Sachais <i>et al.</i> (1977), USA ²²	DB parallel group RCT at 16 centres	Baclofen titrated up to a maximum of 70–80 mg/day on a predetermined schedule. Placebo. Treatment for 5 weeks	N = 166. Spasticity secondary to MS receiving inpatient or outpatient care. Minimum age 18, mean 43 y. Baclofen 85 patients, placebo 81	Baclofen N = 31, placebo N = 29, excluded from statistical analysis for protocol violation, primarily related to concomitant use of disallowed medications, relationship with side-effects not specified	Subjective neurological examination Physician assessment of clinical change. Patient self-evaluation	Statistically significant difference in decreases from baseline values in pain and frequency of flexor spasms, resistance to passive joint movement in the ankle flexion, knee flexion and extension and tendon stretch reflexes in the knee. Overall spastic state improved ($p < 0.001$). Muscle spasms and clonus improved ($p < 0.005$)	3/5
Feldman <i>et al.</i> (1978), USA ¹⁸	DB crossover RCT (long-term follow-up not reported here)	Baclofen increasing 15–80 mg/day. Placebo. 4 weeks on each treatment	N = 33. Age 38–53 y. M:F not stated. Established diagnosis of MS with spasticity for at least 3 months. Duration of MS 3–30 y. Disability varied between ambulatory with spastic gait to quadriplegic	N = 10, due to non-compliance, intercurrent illness, inability to tolerate worsening symptoms	Resistance to passive movement. Spasm frequency. Clonus. Barthel index. Ambulation. Transfer activity. Subjective rating of limb pain. Use of spastic limb	15/23 improved on baclofen, 4/23 on placebo ($p < 0.05$). 9/23 improved on baclofen, 1/23 on placebo ($p < 0.05$). 12/23 improved on baclofen, 1/23 on placebo ($p < 0.001$). No significant difference No significant difference No significant difference No significant difference No significant difference Side-effects of baclofen included drowsiness, dry mouth, paresthesia and blurred vision	3/5

continued

TABLE 2 Baclofen vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Sawa and Paty (1979), Canada ¹¹	DB crossover RCT	Baclofen increasing 10–60 mg/day. Placebo. Treatment for 3 weeks, washout period of 7 days followed by 2nd intervention	N = 21. 6 F, 15 M. Mean ages 36 (F) and 49 (M) y. All patients had clinically definite or presumed MS. Mean duration of MS 9 y (female), 14 y (male). Median spasticity 3 on <i>ad hoc</i> scale of 0–5	N = 3	Spasticity was assessed using the researchers' own grading scale, which ranged from 0 to 5, where 0 represents 'no spasticity' and 5 represents 'in the absence of voluntary contraction, the leg will stay extended for a period of 30 s or more'	On baclofen, 13/18 patients showed an objective improvement in spasticity ($p < 0.001$). No change on placebo. The incidence of side-effects was high, 71% of those on baclofen had side-effects compared with 19% on placebo. Common side-effects were sedation, nausea and vomiting	3/5
Brar <i>et al.</i> (1991), USA ¹⁷	DB crossover RCT	Baclofen alone 20 mg/day. Placebo alone. Baclofen + stretching. Placebo + stretching. 2 weeks on each treatment. Ten-week study	N = 38. Aged 24–54 y. 9 M, 29 F. Clinically definite MS. Duration of disease not stated. Only patients with an EDSS score of <5.5 included. 13 subjects had minimal spasticity in both legs. 17 had minimal spasticity in 1 leg and moderate in the other. The more severely involved leg was used in the data analysis	N = 8, due to exacerbation of symptoms ($n = 4$), transportation difficulties ($n = 2$), side-effects ($n = 1$) and other ($n = 1$)	Quadriceps hypertonicity based on Cybex flexion scores. (Muscle tone.) Ashworth score. Self-assessed functional ability (minimal record of disability)	Significant improvement ($p < 0.05$) on both baclofen treatment and combination therapy when compared with placebo. Difference between baclofen and combination therapy not significant. 9/30 improved on baclofen, 6/30 improved on placebo, 12/30 improved on combination of stretch + baclofen ($p = 0.105$). No significant improvement with either intervention	2/5

continued



TABLE 2 Baclofen vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Orsnes <i>et al.</i> (2000), Denmark ¹⁵	DB crossover RCT	Baclofen increasing 15–45 mg/day. Placebo. 11 days treatment, 2 week wash-out	N = 14. Age 24–57 y. 9 F, 5 M. All MS, of whom 7 were 'clinically definite'. Duration of disease not stated. Patients had a median score of 5 on EDSS at baseline. Median score on Ashworth index of 0.8. All had moderate function and were able to walk unaided for at least 3 minutes	N = 1, for non-medical reasons	Gait analysis using instrumented treadmill and force plate. Voluntary power (MRC scale) Ashworth scale EDSS, AMB, NRS, MSIS ^a	Only one of 12 aspects of gait measured showed improvement, with $p = 0.04$. No significant differences. No significant differences. No significant differences	4/5

^a EDSS, Expanded Disability Status Scale; AMB, ambulation index; NRS, Neurologic Rating Scale; MSIS, MS Impairment Scale.

TABLE 3 Baclofen vs diazepam

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Cartledge <i>et al.</i> (1974), UK ¹³	DB crossover RCT	Baclofen 30 or 60 mg. Diazepam 15 or 30 mg. 2 weeks on each dose, 4 weeks total on each drug	N = 40. Aged 22–61 y. 19 F, 21 M. 34 had MS 'in remission', 2 'probably' had MS. 4 patients did not have MS. All patients had a score of 3 or 4 on the Ashworth scale in one lower limb at least, but mean Ashworth score 2.87	N = 3, none connected with the treatment. There were no withdrawals during low-dose treatment. During high-dose treatment there were 9 patients withdrawn on baclofen and 10 patients withdrawn on diazepam. These patients were included in the data analysis	Ashworth scale, assessed before and after low- and high-dose treatment periods. The assessed limb was not specified. Subjective impression of patients and doctors	No significant difference between the two treatments at low dose. Both drugs produced an improvement (cf. No treatment) at both low and high dose, but this comparison not blinded. 11 patients were unable to tolerate high-dose baclofen, 14 high-dose diazepam. 19/37 patients preferred baclofen, 15/37 diazepam. Doctors preferred baclofen for 18/37 patients, cf. diazepam for 13/37. Patients on diazepam experienced more severe side-effects, especially weakness and sedation	4/5

continued

TABLE 3 Baclofen vs diazepam (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
From and Heltberg (1975), Denmark ¹²	DB crossover RCT	Baclofen 30–120 (mean 61) mg/day. Diazepam 10–40 (mean 27) mg/day. 4 weeks on each drug	N = 17. Age 38–68 y. 10 F, 6 M. All MS. Duration of disease 3–40 y (mean 17.5). All inpatients. All had symptoms of spasticity, predominantly in the lower limbs. Mean Ashworth score in lower limbs 2.5. Only 2 patients could walk, the remaining 14 could either not walk at all or could only walk very short distances	N = 1, due to side-effects, especially sedation on baclofen	Ashworth scale. Change in flexor spasms. Clonus. Walking ability. Side-effects. Subjective overall rating	No significant difference between the two drugs. No difference between the two drugs. No significant difference. Of the 2 patients who could still walk, both improved on baclofen, but one of them deteriorated if given more than 30 mg due to weakness. This same patient deteriorated on 20 mg diazepam also. 1 non-ambulatory patient lost the ability to stand on baclofen due to weakness. Patients experienced greater side-effects on diazepam than on baclofen, especially sedation. 12/16 patients preferred baclofen to diazepam, 4/16 had no preference	3/5

continued

TABLE 3 Baclofen vs diazepam (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Roussan et al. (1985), USA ⁶	DB crossover RCT	Baclofen 15–80 mg (mean 47.3 mg). Diazepam 6–40 mg (mean 28 mg). 5 weeks on treatment, 3 weeks washout	N = 13. 7 had MS. Duration and severity of disease not stated	None	<i>Ad hoc</i> global assessment covering spasm frequency, range of motion, daily activities, pain, by patient and physician, rated 0 to 3+. NB: assessment excluded the impact of side-effects	Patient assessment: greater improvement on diazepam in 3, baclofen in 2, equal in 1, no improvement on either drug in 1. Physician assessment: greater improvement on diazepam in 2, baclofen in 3, equal in 1, no improvement on either drug in 1. Drowsiness in 3 patients on diazepam, 1 on baclofen, at doses used. 1 patient suffered loss of erection on both drugs. Leg oedema in 1 patient on baclofen	2/5

between 18 and 68 years. The duration of disease was not reported in most studies, but where it was, it was reported as between 3 and 30 years. Where stated, all trials recruited both men and women.

The extent of spasticity is variably described, either purely descriptively, using the Ashworth scale or a variant of it, or an *ad hoc* scale.¹¹ In two studies^{12,13} which reported the baseline Ashworth score it was 2.5 and 2.87. Another study¹⁴ reported that all patients had spasticity graded at 3–4 (out of 4). A fourth¹⁵ (using the Ashworth scale in a different way) reported a baseline score of 0.8. Details of the Ashworth and other outcome scoring systems are given in Appendix 2. The extent of disability also appears to have been variable, with one trial¹² recruiting inpatients who could walk only short distances, if at all, and another¹⁶ recruiting only patients who were confined to bed or wheelchair. Others recruited patients with lesser degrees of spasticity, or did not include any details of the level of disability. One study recruited only patients with a baseline Expanded Disability Status Scale (EDSS) of less than 5.5,¹⁷ and another reported that the *median* EDSS was 5 at baseline.¹⁵

Interventions

Baclofen was administered orally in doses of between 10 and 120 mg (the maximum daily dosage is 100 mg). In the majority of studies the dose was increased gradually to a maximum, unless side-effects precluded this. In one,¹⁷ a fixed dose of 20 mg was used. Where diazepam was used as a comparator, the dose was between 6 and 40 mg daily. The duration of all studies was short, with the length of treatment varying between 11 days and 5 weeks.

Outcomes measured

A wide variety of outcome measures was used, involving clinical assessment of spasticity and frequency of spasms. One reported an objective measure of quadriceps tonicity using a Cybex unit. Five studies used the Ashworth scale. One used an *ad hoc* measure of spasticity based on the speed with which a passively flexed leg of a supine patient fell to the bed. Another used a clinical spasticity grading which appears to be very similar to the Ashworth scale. In five of the nine comparisons with placebo, improvement in spasticity was reported as a dichotomous variable (improved or not). Two^{14,15} reported the extent of any improvement in spasticity, as measured by the scale used (although as the Ashworth scale is an ordinal, rather than an interval scale, the analysis is possibly not valid).

Three measured spasm frequency. Four reported the subjective preferences of patients and doctors. Four reported functional ability measured in a variety of different ways. One was primarily a study of the effect of baclofen on gait,¹⁵ which was analysed using a computerised treadmill and force plate. One was primarily an electromyographic (EMG) study,¹⁶ and was reported as such.

Validity of included studies

The DB design of the majority of the studies and the broad range of severity of spasticity of included patients ought to ensure that the results are generalisable to MS patients. In crossover studies of drugs against placebo where the drug has marked therapeutic or side-effects, patients may guess whether they are on active drug or placebo, and may convey this to their physician. Hence it is possible that the blinding was not completely effective. In one crossover study comparing baclofen with diazepam, the comparison with placebo, or control, would not have been blinded.¹³ As non-blinded studies tend to overestimate treatment effects, the implication is that the overall effect of baclofen may be exaggerated.

The validity of the Ashworth scale as a measure of spasticity is not clear. It is an ordinal, rather than an interval scale, so that it is not appropriate to analyse the data by comparing means. However, in most of the studies here the analysis was appropriate.

There was no mention of prior sample size calculations in any of the studies. Their relatively small size implies that they may not have had sufficient power to detect small effect sizes, which would have increased the chance of a Type II error.

Jadad scores were between two and four, with none scoring five.

Summary of direction of effect

In three^{11,18,19} of the crossover studies comparing baclofen with placebo, statistically significantly more patients were reported to have had an improvement in spasticity measured using the Ashworth, or a similar, scale when on baclofen than when on placebo treatment. In a fourth¹⁴ the change in the Ashworth score was significantly greater on baclofen than on placebo. The two studies which used the lowest maximum dose of baclofen were among the three that did not show a statistically significant difference. One¹⁷ (which used the lowest dose of baclofen, 20 mg) reported an improvement in the Cybex score, but not in the

Ashworth score. One of the studies which reported an improvement¹⁸ also reported that more patients experienced an improvement in range of motion and frequency of spasms on baclofen than on placebo.

None of the comparisons between baclofen and diazepam showed a significant difference in the effect of the drugs on the Ashworth score. Nor did the one study that reported on them detect any difference in change in spasm frequency or clonus between the two.¹² Two studies^{12,13} reported an improvement in the Ashworth score (for both drugs) compared with control scores, but this comparison would not have been blind.

In the study of gait,¹⁵ only one of 12 parameters of gait showed an improvement with baclofen treatment, and the *p* value for that comparison was 0.04. Because of the multiple comparisons being made, this would not normally be considered statistically significant (usually one would use a *p* value of 0.001), as it is likely to have occurred by chance. The EMG study did show a decrease in measures of muscle hypertonia on baclofen as compared with placebo.

Preferred treatments

The studies comparing baclofen with placebo did not report patient preferences. The comparisons with diazepam did. In one,¹² 12 of 16 preferred baclofen to diazepam, and four preferred diazepam. In a second,¹³ 19 of 37 patients preferred baclofen, 15 preferred diazepam and three expressed no preference. In the third,⁶ three of seven patients reported greater improvement on diazepam, and two of seven on baclofen.

Impact on function

None of the comparisons with placebo was able to demonstrate any effect of baclofen on functional ability. In some cases, there was even a marked deterioration in functional ability, and it was commented that the spasticity may have been necessary for some residual function. It should be noted, however, that responses to baclofen were variable, and although it may not have been possible overall to demonstrate a consistent effect, there were individual patients who did experience benefit.

Side-effects

Side-effects with baclofen were common. Those most commonly reported were drowsiness, weakness, paraesthesiae and dry mouth. One patient in a crossover study of baclofen and

diazepam suffered loss of erection on both drugs. Side-effects do appear to limit the dose tolerated, but are fewer, and more readily tolerated, than those caused by diazepam.

Summary

The evidence that baclofen leads to an improvement in clinical measures of spasticity in MS as compared with placebo is limited. Objective measures of muscle function (EMG and the Cybex unit) do reveal an effect. However, in the blinded comparisons it is not translated consistently into an effect on subjective measures such as the Ashworth score. There appears to be no difference in the effectiveness of baclofen and diazepam, although baclofen is better tolerated. None of the studies demonstrated any improvement in functional status, but there is some evidence of a preference among patients for baclofen over diazepam.

Dantrolene (Dantrium)

Dantrolene acts directly on skeletal muscle to inhibit contraction of muscle fibres, by inhibiting the release of calcium from the sarcoplasmic reticulum, which is necessary for muscle fibre contraction. Thus, in addition to relieving spasticity, it causes muscle weakness. The cost of dantrolene is £12.32 for 100 25-mg tablets or £43.07 for 100 100-mg tablets.²³ The recommended maximum daily dose is 100 mg four times daily. At this dosage, the average daily cost would be £1.72.

Quantity of research available

Ten papers on the effect of dantrolene on spasticity were identified, of which one was a review. Of the remaining nine, six were retained for inclusion in this review. Three were excluded, one because none of the patients had MS and the other two because only 17/200 and 3/17 patients in each study had MS, and their results could not be separated out.

Details of the six studies included in this review are summarised in *Tables 4* and *5*. Of these, one was an open trial in which both MS and non-MS patients were studied. The other five were all DB RCTs, of which three recruited exclusively MS patients. Four of these were crossover trials, and one a parallel group study (which was reported as a letter). One of the crossover studies compared dantrolene with diazepam, whereas the other five RCTs compared dantrolene with placebo.

TABLE 4 Dantrolene vs placebo

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Gelenberg and Poskanzer (1973), UK ²⁶	DB crossover RCT	Dantrolene 50–200 mg q.d.s. Placebo. 5 weeks treatment, 3 weeks washout, then 5 weeks alternative treatment	N = 20. Age 37–67 y. 9 F, 11 M. All had 'clearly established' MS. Duration of disease not stated. 14/20 were able to walk with difficulty, 5 were bedridden or wheelchair bound and 1 was quadriplegic	0	Clinical including spasticity, strength, clonus and tendon reflexes. Measures not specified	Dantrolene favoured by patients and doctors for 6 patients. 1 additional patient claimed a significant improvement, but this could not be measured objectively. Remaining 13 felt that placebo was better or same as dantrolene, or the side-effects of the treatment negated any benefits. Main side-effects reported were weakness (15), light-headedness (11), nausea (7), dizziness (6) and diarrhoea (6)	2/5
Ladd <i>et al.</i> (1974), Sweden ²⁷	Open trial: 5 patients were evaluated first off drug, then after 5–6 days at the highest dose. 3 patients evaluated in reverse order: first on drug, then off drug	Dantrolene, 25 increasing to 100 mg q.d.s. Duration of study not clear	N = 18. Age 21–54 y. 3 F, 5 M. 8 with 'probable or possible' MS, 10 'normal subjects' as controls. Kurtzke Disability status 3–8. 3/8 wheelchair bound	–	Clinical evaluation of spasticity and clinical status. EMG evaluation of untreated 'normal subjects' and patients on and off treatment	Dantrolene reduced spasticity in 6/8 patients and led to clinical improvement or an improvement in daily living activity in 7/8 patients. 'Marked improvement' in overall clinical condition in 5/8 cases. EMG evaluation suggested that drug patients to increase control over muscle activity as measured by EMG. Weakness was not reported in any patients but some felt tired and dizzy at first	0/5

continued

TABLE 4 Dantrolene vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Tolosa <i>et al.</i> (1975), USA ²⁹	DB parallel group RCT	Dantrolene 25–200 mg q.d.s. Placebo. Treatment for 8 weeks, evaluation at 0, 4 and 8 weeks	N = 23. Ages not stated. Sex not stated. All patients had MS. Duration of disease not stated. Outpatient setting. All patients had spasticity in the lower extremities, 11 were severely disabled and were wheelchair bound. 12 on dantrolene and 11 on placebo	2 (both in dantrolene), 1 due to profound weakness	Spasticity on a scale of 0–6 (0 = flaccid and 6 = extreme resistance)	No clear difference. Reduction in spasticity occurred in 5/12 on dantrolene and 3/11 on placebo. In most cases this improvement was only mild, but was accompanied by an improvement in functional capacity. Concluded that dantrolene was of limited usefulness. Side-effects were only noted in the dantrolene group. Objective weakness was found in 50% of the dantrolene group	3/5
Sheplan and Ishmael (1975), USA ²⁸	DB crossover RCT	Dantrolene 50–100 mg q.d.s. Placebo. 5 weeks treatment, 2 weeks washout	N = 18. 8 with MS. Basis of diagnosis not stated. MS patients aged 34–56 y. Sexes not stated	0	Clinical evaluation of clonus, rigidity and hyperreflexia (no evidence that these scales are validated). Electromechanical evaluation of tendon reflexes and response to tibial nerve stimulation	Clonus reduced in 8/8, abolished in 5/8. Rigidity reduced in 7/7 where present. Hyperreflexia reduced in 8/8, abolished in 6/8. Mechanically measured response to tendon tap and tibial nerve stimulation reduced in all 8/8, by a mean of 45 and 39%, respectively	3/5

continued

TABLE 4 Dantrolene vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Gambi <i>et al.</i> (1983), Italy ²⁴	DB crossover RCT	Dantrolene titrated up to 350 mg/day, mean 30 days. Placebo mean 31 days. 7 days washout	N = 24. 12 with MS. Mean age of MS patients 38 y. 5 M, 7 F. Duration of spasticity, mean 7.2 y	N = 2 from MS group, one with high serum transaminases on admission, one non-evaluable because spasticity too severe	Spasticity, strength, clonus, reflexes, according to <i>ad hoc</i> scales. Physician final assessment of effectiveness	'Dantrolene sodium reduced spasticity of both lower limbs ($p < 0.05$) in comparison with placebo'. Physician's final judgement gave significant difference in benefit with dantrolene ($p < 0.05$). Side-effects (total 13 of all 24 patients): drowsiness (7), nausea (4), gastric pain (4), weakness (3), vomiting (1), malaise (1)	4/5

TABLE 5 Dantrolene vs diazepam

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Schmidt <i>et al.</i> (1976), USA ^{25,30}	DB crossover RCT. The study had 6 evaluation periods: 2 control, and low and high doses of each treatment	Dantrolene 50–300 mg q.d.s. Diazepam 4–20 mg q.d.s. Placebo. Treatment for 4 weeks with 2 week washout periods between treatments	N = 46. Age, sex not stated. All were MS outpatients attending University Clinic. Duration of disease not stated. Moderate – severe spasticity. Mainly ambulatory without severe lower limb weakness Stable for 6 months	N = 4, due to side-effects	Survey of symptoms. Measures of 10 physical functions, assessed by neurologist blind to drug, but not blind to control/low/high dosage. Patient preference. Side-effects	No difference between drugs. Both dantrolene and diazepam reduced spasticity, clonus and reflexes at low and high doses compared with the control. The effect of dantrolene was more dose dependent than with diazepam. 22 preferred dantrolene, 13 preferred diazepam and 7 had no preference. Dose reduced in 15/42 patients due to side-effects. Diazepam decreased hand coordination, reduced hand speed and walking speed. Dantrolene produced weakness at low doses whereas diazepam only produced weakness at high doses. Weakness caused by dantrolene was severe	3/5

In two of the crossover studies comparing dantrolene with placebo, active drug or placebo was given for 5 weeks, followed by a washout (2 weeks in one study, 3 weeks in the other), followed by the alternative. Drug dose was started at 50 mg four times a day, and increased up to 100 or 200 mg four times a day. In the third, dantrolene was titrated up to 350 mg daily, the duration of treatment was a mean of 30 days (31 days for placebo), with 1 week washout between treatments. In the crossover study comparing dantrolene with diazepam, patients were evaluated three times in each study arm. The first evaluation was before starting the drug, the second after 2 weeks of increasing drug dosage ('low dose') and the third after a further 2 weeks at higher dosage ('high dose'). Patients then had 2 weeks washout before evaluation, following which the alternative drug was administered in the same stepped regime. The highest dose of dantrolene administered was 300 mg daily. There were therefore six evaluations in all.

In the parallel group study, patients were randomised to either dantrolene or placebo. Dosage was started at 25 mg four times a day, and increased up to a maximum of 800 mg daily. Evaluation was undertaken at 4 and 8 weeks.

The open trial studied the clinical and EMG effect of dantrolene on eight patients with MS, and compared the EMG results with findings in 10 'normal subjects' (who were not given any drug treatment). The duration of the study was not stated. The dose of dantrolene used was 25, increasing to 100 mg four times daily.

Populations examined

Three of the six studies recruited exclusively patients with MS. One of the RCTs had 12 MS patients out of a total of 24. Another had eight MS patients out of 18, as did the open-label study. One stated that the diagnosis was 'clearly established', and one states that the patients had 'probable or possible' MS. The others do not state the basis on which the diagnosis was made. Duration of disease is stated in only one study,²⁴ in which spasticity had been present for a mean of 7.2 years. The severity of spasticity and extent of disability were variable. In one study,²⁵ patients were mainly ambulatory without severe lower extremity weakness. In another,²⁶ five of the 20 patients were confined to a wheelchair or bed, and one was completely paraplegic. Three studies reported the age and sex of the patients: in one RCT,²⁶ there were 11 men and nine women, aged 39–67, with mean age 49 years; in another,²⁴ of

the 12 patients with MS, there were five men and seven women, with a mean age of 38 years; in the open trial,²⁷ there were five men and four women, aged 21–58, mean 50 years.

Outcomes measured

The parallel group study used a 'semi-quantitative scale' measuring spasticity from 0 to 6. One of the crossover studies did not specify the outcome measures used other than patient preference.²⁶ One used clinical and mechanical tests of musculoskeletal function although there is no evidence that these were validated.²⁸ Another used *ad hoc* scales of spasticity, strength, clonus and reflexes.²⁴ The other crossover study²⁵ used clinical and 'simple mechanical equipment' to assess 10 physical functions. As this was the study which evaluated high and low doses of both dantrolene and diazepam, and involved a control evaluation (drug free), a total of 90 separate comparisons were reported on, which must have increased the chance of a Type I error. For this reason, the authors only considered as 'statistically significant' those comparisons in which the difference is quoted as statistically significant with $p < 0.001$. Further, in this study, neither patient nor evaluating physician can have been blind to whether the patient was taking a low or high dose of drug. Hence the only comparisons for which blinding was preserved were between drugs, not between dosage levels of the drugs or between drugs and 'control'.

In three of the crossover studies, patients were asked to express a preference for either dantrolene or diazepam, or dantrolene or placebo.^{24,26}

The open trial used an unspecified clinical assessment of spasticity and overall clinical status, and an EMG evaluation using four tests of the patient's ability to control muscular activity.²⁷

Validity of included studies

Although there appears to have been some variability between the study populations in terms of the extent of disability and disease duration, there is no reason to think that the populations studied were not typical of MS patients. In crossover studies of drugs against placebo where the drug has marked therapeutic or side-effects, patients may guess whether they are on active treatment or placebo, and may convey this to the evaluating physician. Thus, in addition to the failure of blinding as to dose levels in one study, mentioned above, there may have been a failure of blinding in the crossover study which compared dantrolene with placebo. Unblinded studies are

more likely than blinded studies to report positive effects. The Jadad scores for the six studies are low, with one score of 4, three scores of 3, one of 2 and one²⁷ of zero.

There is no mention of sample size calculation in any of the studies. The relatively small size of the studies implies that they may not have had sufficient power to detect small effect sizes, which would increase the chance of a Type II error.

The open trial, being neither blinded nor controlled, is of questionable validity.

Summary of direction of effect

One of the crossover comparisons with placebo did not specify any objective outcomes. The others reported benefit in both clinical and electromechanical measures on dantrolene. In the comparison with diazepam there was no consistent effect of dantrolene other than an 'improvement' in 'reflexes' (it is impossible to determine the clinical significance of the quantitative results given with regard to this). Dantrolene at both low and high doses is reported (at $p < 0.001$) to lead to improved spasticity, reflexes, clonus and deltoid strength compared with placebo but, as noted above, neither patient nor physician would have been blind for this comparison. In the parallel study, a reduction in spasticity scores was observed in five of 12 patients on dantrolene and in three of 11 on placebo. The improvement in spasticity was said to be only mild except for one case.

The open trial reported an improvement in clinical status in five of eight patients treated.

Preferred treatments

In one of the crossover comparisons against placebo, seven of 20 patients expressed a preference for dantrolene over placebo, four preferred placebo (because of the avoidance of side-effects) and nine had no preference. In the crossover study of dantrolene compared with diazepam, out of the 42 patients who completed the study, 22 preferred dantrolene, 13 diazepam and seven neither drug.²⁵

Impact on function

Very little detail is given about any effect on function. In both of the crossover studies against placebo, some ambulatory patients were said have improved gait and improved activities of daily living. Four patients were confined to wheelchairs, and relief of spasticity was said to have enabled them to move around more, and to be beneficial to their carers. In the parallel group study, the one

patient who was reported to have benefited significantly from dantrolene was said to have had an improvement in functional capacity, but further details were not given. The open trial reports that in two patients transfers were easier, and in three gait was improved, although the extent of this was not stated.

Side-effects

Eight out of the total of 115 patients recruited in these studies dropped out because of the side-effects experienced when taking dantrolene. The main side-effect reported in all studies was weakness. This affected more than 50% of patients in all studies. The extent to which this was disabling appears to have been variable. In one study weakness produced even at low doses was so severe that patients began to fall as their legs buckled, and this side-effect stayed with them for the duration of the treatment. Other commonly reported side-effects included light-headedness, dizziness, nausea and diarrhoea. In the one study in which they were asked to express a preference, four out of 20 patients expressed a preference for placebo, because of the lack of side-effects.²⁶

Summary

Dantrolene appears to have a moderate effect on spasticity. However, its value is severely restricted owing to the frequency of unwanted side-effects, in particular weakness and gastrointestinal symptoms.

Tizanidine (Zanaflex, Sirdalud)

Tizanidine is a short-acting muscle relaxant which acts on the α_2 -adrenergic receptors. It is indicated for acute and intermittent management of increased muscle tone associated with spasticity. The cost of tizanidine is £89.70 for 120 4-mg tablets.²³ The maximum daily dosage is 36 mg and the recommended daily dosage is 24 mg. At this recommended dosage the average daily cost would be £4.49.

Quantity of research available

Sixteen papers on the use of tizanidine in the treatment of spasticity were identified. Of these, one was a review, one was a letter and the third was a very poor quality, selective meta-analysis. These three were excluded, leaving 12 DB RCTs and one randomised trial which was described as 'partially blind'.³¹ Of these, two are studies of the effect of single doses of the drug, compared with placebo. The other 11 are studies of medium-term use of the drug (5–15 weeks), three being comparisons with placebo, one with diazepam, six

with baclofen and one with both baclofen and tetrazepam. Details of the studies included in this review are given in *Tables 6–9*.

Study designs

Of the 12 DB RCTs included, nine were parallel group studies and three were crossover studies (two comparing tizanidine with baclofen, one with placebo). The two single-dose studies involved 142 and 17 patients. The larger one was a dose–response study comparing the effects of placebo and 8 and 16 mg of tizanidine. The smaller one was a crossover study in which patients were given placebo, 2, 4 and 8 mg of tizanidine on four separate days, with a washout period in between. There was one dropout in the smaller study and two in the larger. In both cases muscle tone was assessed using the Ashworth scale and the pendulum test, although not in the same way.

Populations examined

All but one trial included involved only patients with MS; one trial included 32 patients with MS out of 36 subjects. Study sizes varied between 16 and 220 patients. In the majority of cases these were ‘clinically diagnosed’, with or without laboratory support. One study included patients with ‘probable MS’. The mean age of patients in the studies was between 42 and 54 years with, in most cases, a majority of women over men. The mean duration of disease was reported in five studies, and varied from 7 to 15 years (within this, there were wide variations for individual patients). The duration of spasticity was reported in seven studies, varying between ‘at least 2 months of stable spasticity’ to between 6 and 8 years.

Four studies reported the severity of spasticity at baseline, using the Ashworth score, two recruiting only patients with a score of ≥ 2 , one recruiting patients with scores of 1–4 and another with scores of 2–3. Three other studies described the baseline spasticity as moderate or severe, one stated that patients were ‘disabled by spasticity’ and two did not characterise the severity at all. The extent of overall disability varied substantially between the populations studied. Three studies reported this in terms of the EDSS (1.5–9.5 in one, 3.5–7 in another, 4–7 in the third). Others reported the level of disability in qualitative terms, ranging from ‘interfering with activities of daily living’ to ‘seriously handicapped’. One included only hospitalised patients.³²

Intervention

The doses of tizanidine used in the single-dose studies were between 2 and 16 mg. In the longer

term studies it was between 2 and 36 mg per day. Comparator doses of diazepam were 15 mg per day (mean), and of baclofen 15–80 mg per day. In the trial of tizanidine against baclofen and tetrazepam,³³ the dose of each drug used was not explicit.

Outcomes

In most of the studies the outcomes measured included the Ashworth score, although it was not used consistently in all studies. In some cases the individual scores for single muscle groups were reported. In others, the scores for a number of muscle groups were aggregated to give an overall score. Other outcomes measured included the frequency of muscle spasms, muscle strength, the pendulum test and measures of functional ability.

Validity of included studies

As far as can be ascertained, in all cases the conduct of the studies was robust. The DB RCT design ought to ensure internal validity. Although there was no explicit consideration of sample size in any of the studies, the sample sizes in the studies of tizanidine were generally much larger than those for the older drugs such as baclofen or diazepam.

The summation and averaging of Ashworth scores (an ordinal scale) which was done in some of the studies^{34,35} was statistically inappropriate.

The Jadad scores for studies of tizanidine were generally higher than those obtained for studies based on other drugs in this review. The average Jadad score for the 13 studies reviewed here is 3.5 with no single study scoring <3 . The higher quality of these studies may reflect the fact that tizanidine is much newer to market than the other drugs included in this review.

Summary of direction of effect

Both the single-dose studies showed a statistically significant, dose-dependent improvement in the result of the pendulum test. The larger study showed a dose-dependent improvement in the Ashworth score (up to four points, when the total score is measured up to 16), but the improvement in Ashworth score in the smaller study did not appear to be statistically significantly different to that seen with placebo. Neither study included any functional assessment. The clinical effects appear to last until 3 hours post-dose, but to have faded by 6 hours.

The two longer-term studies comparing tizanidine with placebo involved 187 and 220 patients, with

TABLE 6 Tizanidine vs placebo

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Lapierre <i>et al.</i> (1987), Canada ³⁶	DB parallel group RCT	Tizanidine titrated over 3 weeks to max. of 32 mg/day, (mean 18.4 mg/day) maintained for 5 weeks, vs placebo	N = 66. All with definite MS. Mean age 47.6 y (T), 43.8 y (P). 33 M, 33 F. Mean disease duration 15.2 y (T), 11.6 y (P). Spasticity present for 6–8 y, stable for at least 2 months. 'Generally moderate to severe'	N = 7. 4 on tizanidine due to lack of effect or side-effects, 1 due to relapse of MS. Two on placebo, one due to intercurrent illness, one to side-effects	Kurtzke score. AMB. Upper extremity index. Limb tone. Tendon reflexes. Muscle strength. Electrophysiological parameters. Overall assessment made by investigators based on patients' own impression and objective findings. Side-effects	Improved in three of each group, deteriorated in five of placebo group, but overall no change in either group. Small improvement in treated group, not significantly different to placebo. Small improvement in treated group, not significantly different to placebo. 'Cumulative limb tone' improved more in the treated group than in the placebo group. Improved more in treated than placebo group. Mild improvement in both groups overall, but one-third in each group had increased weakness. No change in either group in any of the parameters measured. Improvement in 69% of treated group, 38% of placebo group. Drowsiness and dry mouth reported in 48%, 27% of tizanidine patients, decreasing with treatment	4/5

continued

TABLE 6 Tizanidine vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
UK Tizanidine Trial Group (1994), UK ³⁵	DB parallel group RCT	Tizanidine 31 mg. Placebo 35 mg. 3 weeks run-in. 9 weeks main stage	N = 187. Mean age 47 y. 121 F, 65 M. 94 tizanidine, 93 placebo. Clinically definite, lab. supported or probable MS. Mean duration of MS 13 y. Mean duration of stable spasticity 3 y. Mostly mild–moderate spasticity (Ashworth score 2–3). EDSS scores from 1.5–9.5. Some were bedridden, most were ambulatory	N = 32. 19 tizanidine, 13 placebo. However, more than this violated the protocol	Muscle tone (Ashworth score). Muscle spasms and pain. Muscle weakness (MRC scale). Walking. EDSS. Intermediate functions. Subjective assessment of efficacy	21% reduction muscle tone on tizanidine ($p = 0.004$). Differences not significant No significant differences No significant differences No significant differences There was a trend in favour of tizanidine but this was not statistically significant. 63% of patients on tizanidine rated their treatment as effective compared with 45% of those on placebo	4/5
Smith <i>et al.</i> (1994), USA ³⁹	DB parallel group RCT	Tizanidine 2–36 mg. Placebo. 15 weeks	N = 220. Mean ages 46 and 45 y in tizanidine and placebo groups. 125 F, 83 M. 111 tizanidine, 109 placebo, 159 completed. Clinically definite MS. Duration of MS 11 y average (range 4 months – 40 y). Duration of spasticity not stated. Ashworth score 1–4. 'Significant discomfort or functional impairment'	N = 61. 28 tizanidine, 33 placebo	Muscle tone (Ashworth score). Spasms and clonus (patient's diary). Muscle strength (MRC scale)	No differences between groups. Trend towards a reduction in spasms and clonus with tizanidine group. <i>Post hoc</i> non-parametric analysis showed a reduction in median response ratio ($p = 0.028$). Strength maintained in both groups	3/5

continued

TABLE 6 Tizanidine vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Emre <i>et al.</i> (1994), Switzerland ⁴⁰	DB crossover RCT	Tizanidine 2, 4, 8 mg. Placebo. Single dose only	N = 17. Mean age 43 y (24–58). 13 F, 4 M. Clinically definite MS. Duration of MS not stated. Duration of spasticity 70 months (12–180 months) Extensor spasticity had minimum score of 2 on Ashworth scale. None were bedridden	N = 1, due to baseline spasticity declining below minimum	Relaxation index (R2) based on the Wartenburg pendulum test. Muscle strength (MRC scale). Muscle tone using the Ashworth scale	Dose-related response in R2 in the tizanidine group. No change. There appears to be a moderate change but the paper is not explicit	5/5 Small Sample size
Nance <i>et al.</i> (1997), USA and Canada ³⁴	DB parallel group RCT dose – response study	Tizanidine 8 or 16 mg. Placebo. Single dose only	N = 142. Ages not stated. 86 F, 56 M overall. 45 tizanidine 8 mg, 49 tizanidine 16 mg, 48 placebo. Clinically definite MS. Duration of disease not stated. Duration of spasticity not stated. Minimum score of 2 on Ashworth scale for lower extremity. Moderate/severe disability. EDSS scores 3.5–7	N = 2. 1 due to hypotension after tizanidine	Muscle tone using Ashworth scale and the pendulum test	In the tizanidine group the Ashworth score decreased by an average of 2 after 1 h and 1.6 after 3 h ($p < 0.001$). Change in score correlated with a change in plasma concentration. Tizanidine produced a significant improvement in the pendulum test ($p < 0.001$). Greater improvement in the 16-mg group than with the 8-mg group	3/5

TABLE 7 Tizanidine vs diazepam

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Rinne (1980), Finland ⁴¹	DB parallel group RCT	Tizanidine 18 mg. Diazepam 22.5 mg (maximum doses). 6 weeks	N = 30. Age 42 (T), 40 (D) y (mean). 19 F, 11 M. 15 in each group. Basis of diagnosis not stated. Duration of disease 7 (T), 12 (D) y. Duration of stable spasticity at least 1 y. Spasticity 'moderate-severe'. Extent of disability not stated	N = 4. All 4 were on diazepam and had to be withdrawn owing to adverse reactions	Ashworth scale	9 patients in each group showed an improvement in spasticity and there was no significant difference between the two groups. Overall the tolerability of tizanidine was significantly greater than diazepam	3/5

TABLE 8 Tizanidine vs baclofen

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Smolenski <i>et al.</i> (1981), Switzerland ³²	DB parallel group RCT	Treatments titrated up to an 'optimal' daily dose. Baclofen 10–80 mg/day. Tizanidine 8–36 mg/day. Treatment for 6 weeks. Washout period 3–5 days	N = 21. Hospitalised MS patients. 10 M, 11 F. Aged 42–73, mean 54 y	None	Muscle tone and spasms, and muscle strength. Subjective neurological examination (Kurtzke scoring) and functional assessment (Pedersen). Physician's and patient's assessment of change. Physician's assessment of clinical change. Patient self-evaluation	No statistical analysis of efficacy outcomes. Most patients showed overall improvement, similar between treatment groups. Little change evident. Tendency for night-time spasms and bladder function to show more improvement in the tizanidine group, otherwise little difference between groups	3/5
Newman <i>et al.</i> (1982), UK ³⁷	DB crossover RCT	Dosage increased over 2 weeks to Baclofen 40 mg, tizanidine 16 mg daily, then maintained for a further 1 month. Washout 1 week	N = 36 (32 with MS). 'Neurologically stable and disabled by spasticity'. 26 patients assessed, 12 M, 14 F, mean age 45.9 y, duration of disease 9 y	N = 10 (6 on baclofen, 4 on tizanidine), 8 because of side-effects, two because of protocol violation	Neurological disability – Kurtzke scale Functional disability – Pederson functional assessment Ashworth score Subjective assessment by patient and examiner	Neither drug led to any difference in Kurtzke or Pederson scales. No change in upper limb tone. In lower limb some improvement in tone but no significant difference between the two drugs. When change in Ashworth scores for all 4 lower limb joints added, significant improvement seen when on tizanidine, not on baclofen. Neither drug favoured in patients' diaries	4/5

continued

TABLE 8 Tizanidine vs baclofen (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Stien <i>et al.</i> (1987), Norway ⁴²	DB parallel group RCT	Tizanidine 23 mg. Baclofen 59 mg. 6 weeks	N = 40. Median ages 50 (T), 45 (B) y. 21 F, 17 M. Clinically definite MS. Disease duration median 14 (T), 13 (B) y. Stable for >3 months. Severity of spasticity not explicitly stated. Severely handicapped – nearly all bed-ridden or in wheelchairs	N = 2. One in each arm of the study	Clinical assessment: Clonus activity. Ashworth score. Neurological disability – Kurtzke scale. Functional disability – Pederson functional assessment. Neurologist estimate of muscular resistance and antispastic efficacy	No difference between drugs and no overall reduction in clonus activity (8 of the patients treated with baclofen experienced an increase in clonus activity. No difference between drugs. Neither drug led to any difference in Kurtzke or Pederson scales. Regardless of the treatment, where spasticity did improve it had no effect on functional assessment or daily life activities. Both drugs judged to have had an antispastic effect in at least half the patients	4/5
Eyssette <i>et al.</i> (1988), France ⁴³	DB parallel group RCT	Tizanidine 24 mg. Baclofen 60 mg (maximum doses). 2 weeks dose titration, 6 weeks stable dose (8 weeks total)	N = 100. Mean age 47 (range 23–79) y. 43 F, 57 M. All MS, basis of diagnosis not stated. Duration of disease not stated. Duration of spasticity not stated. All with spasticity symptoms, severity not stated. 60 patients were bedridden (33 T, 27 B)	N = 2. 1 patient in each group withdrew due to side- effects	Overall assessment of efficacy of treatment. Locomotor function. Patient's state in bed and in a chair. Flexor spasms. Muscle tone	No significant difference. Tizanidine and baclofen improved functional status in 80% and 76% of cases, respectively. In ambulatory patients there was no change in walking distance. At the end of the trial 31 in the tizanidine group were bedridden (a reduction of 2) and 29 baclofen patients were bedridden (an increase of 2)	3/5

continued

TABLE 8 Tizanidine vs baclofen (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Rice <i>et al.</i> (1988), Canada ^{38,44}	DB crossover RCT	Tizanidine 6–32 mg daily. Baclofen 15–80 mg daily. 3 weeks titration. 5 weeks max. dose on each drug with washout period in between	<i>N</i> = 66 entered. Mean ages 50 (T–B), 53 (B–T). 31 F, 31 M. 48 completed. Clinically definite MS. Duration of disease not stated. Both groups had spasticity for 8 y, predominantly in the legs, stable for >2 months. All had moderately severe spasticity. Spasticity 'interfered with activities of daily living'	<i>N</i> = 18, 2 due to non-compliance, 7 stopped taking baclofen owing to weakness, 4 stopped tizanidine owing to weakness, 5 stopped baclofen due to nausea	Spasticity measured on 6-point ordinal scale. Kurtzke functional scale. Pederson functional disability scale. Overall evaluation of efficacy by investigators, physio therapists and patients	No significant differences between groups. No change from baseline. Patients, no difference. Investigators and physiotherapists both rated baclofen as more effective overall (<i>p</i> = 0.05, Fisher's exact test). Side-effects: more muscle weakness experienced by those on baclofen (statistically significant at 0.01); patients reported no difference in tolerability between drugs, physicians and physiotherapists reported tizanidine better tolerated than baclofen	3/5
Hoogstraten <i>et al.</i> (1988), The Netherlands ³¹	'Partially blind' randomised, crossover study	Dosage titrated over 2–3 weeks, then held for 4 weeks. 3 day washout. Baclofen dose ranged from 15 to 60 mg daily, tizanidine from 12 to 24 mg daily	<i>N</i> = 16. All with MS. All with spasticity for >2 months. 10 M, 6 F. Scored 4–7 on EDSS	<i>N</i> = 5	Kurtzke EDSS. Incapacity status. AMB. Ashworth scale. Patient-evaluated overall spastic condition, impairment of activities, overall disability status, etc. 'Based on these ... the efficacy and tolerance of the treatment were evaluated ...'	Overall, both drugs noted to be effective, with no significant difference between them. Muscular weakness reported in 6 patients on baclofen, none on tizanidine. Of the five withdrawals, one started on baclofen and withdrew because of falls due to weakness, one started on tizanidine and withdrew because of depression, three started on tizanidine, then withdrew in second treatment period on baclofen because of falls	3/5

TABLE 9 Tizanidine vs baclofen vs tetrazepam

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Pellkofer <i>et al.</i> (1989), Germany ³³	DB parallel group RCT	Tizanidine 2-mg capsules, <i>n</i> = 15. Baclofen 5-mg capsules, <i>n</i> = 16. Tetrazepam 25-mg capsules, <i>n</i> = 16. Number (dose) taken not specified. 35 days treatment	<i>N</i> = 47. All with MS >2 y duration, stable for >2 months. 18 M, 29 F. Aged 18–65 y	3 dropouts in the baclofen and tizanidine groups due to ineffectiveness!	Kurtzke scale. Pedersen scale. Ashworth score. Zerlson health status scale. Dotes scale	Spasticity reduced on all three drugs, but no differences between them in terms of effectiveness. Side-effects: tizanidine 3 hypotonia, somnolence; baclofen, 1 weakness, somnolence, dizziness; tetrazepam, 3 weakness, dizziness, somnolence	4/5

32 and 61 dropouts, respectively. Tizanidine was given in doses up to 36 mg daily. In both cases the primary outcome measure was a variant of the Ashworth score (not measured in the same way in both studies). In the larger study, the frequency of muscle spasms and clonus was also used as a primary outcome measure.

One study showed a reduction in muscle tone on treatment that was significantly greater than placebo, the other did not. In the former study, the baseline muscle tone in the placebo group was slightly lower than in the treated group. It should be noted that the summation and averaging of the Ashworth scores for individual muscle groups (the basis on which efficacy was claimed) was statistically inappropriate, as it is measured on an ordinal scale. In the latter, the muscle tone was slightly higher in the placebo group at baseline, and the fall on placebo was greater than expected. In this study, which assessed muscle spasm and clonus as a primary outcome measure, there was a greater reduction in spasms and clonus in the treated than in the placebo group. A non-significant trend towards this was reported in the other study. Neither study demonstrated any difference in functional status between the placebo and treatment groups.

The third placebo-controlled RCT of prolonged tizanidine use reported no significant difference between active drug and placebo in Kurtzke EDSS score, AMB, 'upper extremity index' muscle strength or electrophysiological parameters. However, there was significant improvement in limb tone, tendon reflexes and in the overall assessment made by the investigators in the drug-treated as compared with the placebo group.³⁶

Comparison with diazepam

One study compared tizanidine with diazepam in MS patients. Thirty patients were treated with tizanidine (mean dose 14.3 mg) or diazepam (mean dose 15.0 mg) for 6 weeks. Clinical effect is said to have been assessed using Ashworth score, although how this was done is not explicit. Overall there was no difference between the two drugs.

Comparison with baclofen

Six studies compared tizanidine with baclofen, including the 'partially blind' study. The study sizes varied from 16 to 100 patients, with between 0 and 18 dropouts. Tizanidine dosage was in the range 6–36 mg daily, for a duration of 6–8 weeks. Two were crossover studies. The severity of spasticity of patients in these trials appears to have been greater than in the placebo controlled trials,

with a high proportion moderately or severely affected and in the largest trial the majority were bedridden.

Outcome was assessed using a variety of measures, including the Ashworth score, the Kurtzke and Pedersen functional assessment scales, and investigator, physiotherapist and patient preference. Overall, there was no difference between the two drugs on any of the outcomes assessed, with the exception of one study³⁷ which reported a significant improvement in the combined Ashworth score for four lower limb joints on tizanidine but not on baclofen. Moreover, in the three of the four studies which assessed functional improvement using the Kurtzke and Pedersen scales, neither drug produced any improvement in functional status.

Comparison with baclofen and tetrazepam

One study consisted of a three-way comparison between tizanidine, baclofen and tetrazepam.³³ Unfortunately, although the capsule strength is stated, the number of capsules (and hence total dose) taken by each patient is not explicit. There were three dropouts (out of 16 and 15 patients) in each of the baclofen and tizanidine groups due to ineffectiveness of the treatment. Spasticity is reported to have been reduced in each of the three groups, but there was no difference between them in terms of effectiveness.

Side-effects

Overall, tizanidine is well tolerated. The most frequent side-effects mentioned are drowsiness and a dry mouth. In general, a reduction in spasticity was not achieved at the expense of muscle strength. Tizanidine was better tolerated than diazepam, but there appeared to be little difference between it and baclofen in terms of frequency and severity of side-effects. However, in the only study where individual overall preferences were assessed, patients, investigators and physiotherapists preferred baclofen over tizanidine.

Summary

Tizanidine is effective in both the short and medium term, in comparison with placebo. When compared with diazepam or baclofen, tizanidine appears to be equally effective. Whilst tizanidine has a significant effect on muscle tone, frequency of spasms and clonus, it has not been shown to have an effect in terms of functional ability. However, in view of the relatively small sample sizes of these studies, there may be a real

difference in effect that has been missed (Type II error). Most of the studies show no difference between tizanidine and its comparators in terms of causing muscle weakness. Only two studies found that tizanidine is less likely to cause muscle weakness than alternative drug therapy.^{31,38}

Diazepam

Diazepam reduces muscle tone by suppressing sensory impulses from muscles and skin receptors, potentiation of GABA action post-synaptically and inhibition of excitatory descending pathways. The cost of diazepam (Valium) is £8.58 for 100 10-mg tablets.¹⁰ The maximum recommended dosage is 60 mg per day. At this dosage the average daily cost would be £0.52. A more typical dose of 20 mg per day would cost just £0.17 per day.

Quantity of research available and study characteristics

One single blind comparison of diazepam with placebo was identified,⁴⁵ together with six RCTs comparing diazepam with other active drugs. Two crossover studies compared diazepam with baclofen and one with dantrolene, and one parallel group study compared it with tizanidine. All of these used diazepam as the comparator rather than the main intervention, and so are duplications of other sections of this report (hence the results are only summarised here). Two studies compared diazepam with ketazolam and placebo. Details of the seven studies included in this review are given in *Tables 10–14*.

Populations examined

The trial of diazepam against placebo included 21 patients, of whom only four had MS (although the results for these patients were reported separately). The disease was of 9–11 years' duration, causing severe spasticity of the legs. The age range was 49–62 years.

Of the two studies comparing diazepam with baclofen, one recruited 40 patients, of whom 34 had definite and two probable MS. The Ashworth score was 3 or 4 in at least one lower limb. The other study recruited 17 patients with MS of on average 17.5 years' duration. There was one dropout. Only two of the remaining 16 could walk. The study comparing diazepam with dantrolene recruited 46 MS patients from a university outpatient clinic. They were said to be mainly ambulatory, with moderate to severe spasticity, but without severe lower limb weakness. Age, sex and

duration of disease were not stated. The study comparing diazepam with tizanidine again recruited only MS patients with mean disease duration 9 years (basis of diagnosis not stated). The mean age was 41 years, with 19 women and 11 men. Spasticity was described as 'moderate to severe', but the extent of disability was not otherwise stated.

Of the two trials comparing diazepam with ketazolam, one recruited 50 patients, of whom 24 had MS, described as stable, severe and chronic. Their ages ranged from 18 to 68 years. The other recruited 17 patients, all of whom had 'chronic MS and severe spasticity'.

Outcome measures

The comparison with placebo reported only the physician and patient overall assessment. Three of the other studies used the Ashworth scale. In one case¹² this was supplemented by further clinical evaluation. The comparison with dantrolene²⁵ used measures of 10 physical functions, as assessed by a neurologist, using clinical and 'simple mechanical' measures. The comparisons with ketazolam reported summary results of multiple outcomes, including resistance to passive stretching, range of motion, reflexes, clonus, muscle power and pain.

Validity

Little weight can be put on the comparison with placebo, as it was single blind only, and reported only four patients with MS. With the exception of the study in which diazepam was compared with dantrolene,²⁵ in which patients and evaluators were not blind to drug dose level (although they were to drug), the other study designs appear to have been robust. A further criticism of that study is that there were multiple outcome measures, and multiple comparisons, which must have increased the chance of a Type I error. Two of the studies reported four dropouts each, due to side-effects. There was no explicit consideration of sample size in any of the studies, and in most cases they appear to have been a convenience sample. Small sample sizes imply reduced power and, thus, may increase the chance of a Type II error.

Summary of the direction of effect

In both of the comparisons between baclofen and diazepam, an improvement in the Ashworth score on treatment with diazepam compared with baseline was observed. However, no difference was identified between the two drugs for any of the measures used.

TABLE 10 *Diazepam vs placebo*

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Neill (1966), UK ⁴⁵	Single-blind placebo-controlled crossover study	Diazepam 16 mg/day, increasing after 1 week to 24 mg/day, continued for a further 1 week. Placebo. No mention of washout between treatments	N = 21. 4 with MS, 9–11 y duration, with severe spasticity of the legs. 3 M, 1 F. 49–62 y	None	Physician assessment (<i>ad hoc</i> scale). Patient assessment	One patient improved a lot on diazepam, two improved a little on placebo, one deteriorated on placebo. 3 of 4 patients said they felt they had greater improvement of spasms on diazepam	1/5

TABLE 11 Diazepam vs baclofen

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
From and Heltberg (1975), Denmark ¹²	DB crossover RCT	Baclofen 30–120 (mean 61) mg/day. Diazepam 10–40 (mean 27) mg/day. 4 weeks on each drug	N = 17. Age 38–68 y. 10 F, 6 M. All MS. Duration of disease 3–40 y (mean 17.5). All inpatients. All had symptoms of spasticity, predominantly in the lower limbs. Mean Ashworth score in lower limbs 2.5. Only 2 patients could walk, the remaining 14 either could not walk at all or could only walk very short distances	N = 1, due to side-effects, especially sedation on baclofen	Ashworth scale. Change in flexor spasms. Clonus. Walking ability. Side-effects. Subjective overall rating	No significant difference between the two drugs. No difference between the two drugs. No significant difference. Of the 2 patients who could still walk, both improved on baclofen, but one of them deteriorated if given more than 30 mg due to weakness. The same patient deteriorated on 20 mg of diazepam also. One non-ambulatory patient lost the ability to stand on baclofen due to weakness. Patients experienced greater side-effects on diazepam than on baclofen especially sedation. 12/16 patients preferred baclofen to diazepam, 4/16 had no preference	3/5

continued

TABLE II Diazepam vs baclofen (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Cartlidge et al. (1974), UK ¹³	DB crossover RCT	Baclofen 30 or 60 mg. Diazepam 15 or 30 mg. 2 weeks on each dose, 4 weeks total on each drug	N = 40. Aged 22–61 y. 19 F, 21 M. 34 had MS 'in remission', 2 'probably' had MS. 4 patients did not have MS. All patients had a score of 3 or 4 on the Ashworth scale in one lower limb at least, but mean Ashworth score 2.87	N = 3, none connected with the treatment. There were no withdrawals during low-dose treatment. During high-dose treatment there were 9 patients withdrawn on baclofen and 10 patients withdrawn on diazepam. These patients were included in the data analysis	Ashworth scale, assessed before, and after low- and high-dose treatment periods. The assessed limb was not specified. Subjective impression of patients and doctors	No significant difference between the two treatments at low dose. Both drugs produced an improvement (cf. No treatment) at both low and high dose, but this comparison not blinded. 11 patients were unable to tolerate high-dose baclofen, 14 high-dose diazepam. 19/37 patients preferred baclofen, 15/37 diazepam. Doctors preferred baclofen for 18/37 patients, cf. diazepam for 13/37. Patients on diazepam experienced more severe side-effects especially weakness and sedation	4/5

TABLE 12 Diazepam vs tizanidine

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Rinne (1980), Finland ⁴¹	DB parallel group RCT	Tizanidine 18 mg. Diazepam 22.5 mg (maximum doses). 6 weeks	N = 30. Age 42 (T), 40 (D) y, mean. 19 F, 11 M. 15 in each group. Basis of diagnosis not stated. Duration of disease 7 (T), 12 (D) y mean. Duration of stable spasticity at least 1 year. Spasticity 'moderate-severe'. Extent of disability not stated	N = 4. All 4 were on diazepam and had to be withdrawn owing to adverse reactions	Ashworth scale	9 patients in each group showed an improvement in spasticity and there was no significant difference between the 2 groups. Overall the tolerability of tizanidine was significantly greater than that of diazepam	3/5

TABLE 13 *Diazepam vs dantrolene*

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Schmidt (1976), USA ²⁵	DB crossover RCT. The study had 6 evaluation periods – 2 control, and low and high doses of each treatment	Dantrolene 50–300 mg q.d.s. Diazepam 4–20 mg q.d.s. Placebo. Treatment for 4 weeks with 2 week washout periods between treatments	N = 46. Age, sex not stated. All were MS outpatients attending University Clinic. Duration of disease not stated. Moderate – severe spasticity. Mainly ambulatory without severe lower limb weakness. Stable for 6 months	N = 4, due to side-effects	Survey of symptoms. Measures of 10 physical functions, assessed by neurologist blind to drug, but not blind to control/low/high dosage. Patient preference. Side-effects	No difference between drugs. Both dantrolene and diazepam reduced spasticity, clonus and reflexes at low and high doses compared with the control. The effect of dantrolene was more dose dependent than with diazepam. 22 preferred dantrolene, 13 preferred diazepam and 7 had no preference. Dose reduced in 15/42 patients due to side-effects. Diazepam decreased hand coordination, reduced hand speed and walking speed. Dantrolene produced weakness at low doses whereas diazepam only produced weakness at high doses. Weakness caused by dantrolene was severe	3/5

TABLE 14 Diazepam vs ketazolam

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Basmajian <i>et al.</i> (1984), Canada ⁴⁶	DB crossover RCT	Ketazolam (K) (3 × 10 mg/day for 7 days increased to 3 × 20 mg/day for 7 days). Diazepam (D) (3 × 5 mg/day for 7 days increased to 3 × 10 mg for 7 days). Placebo (P) (dose doubled after 7 days). 2 weeks treatment. 1 day washout period	N = 50, of whom 24 had MS. Age range 18–68 y (all patients). 14 M, 10 F (MS only). All MS patients 'stable, severe, chronic, stage. Almost all patients having had spasticity for 1 year	(MS patients only.) N = 4	Resistance to passive stretching. Range of motion. Reflexes. Clonus. Muscle power. Pain, motor status, spasm and function (subjective impression). EMG	(MS patients only.) (Summary results for all outcomes reported only.) K vs D = no significant difference. K vs P = statistically significant difference ($p = 0.05$) in favour of K. D vs P = statistically significant difference ($p = 0.05$) in favour of D.	4/5
Basmajian <i>et al.</i> (1986), Canada ⁴⁷	DB crossover RCT	Ketazolam (K) [1 × 10 mg + 2 × 10 mg placebo (P)/day for 7 days increased to 1 × 20 mg + 2 × 20 mg P/day for 7 days]. Diazepam (D) (3 × 5 mg/day for 7 days increased to 3 × 10 mg for 7 days). Placebo (P) (dose doubled after 7 days). 2 weeks treatment. 1 day washout period	N = 17. All with 'chronic MS and severe spasticity'. No further details reported	N = 3	Resistance to passive stretching. Range of motion. Reflexes. Clonus. Muscle power. Pain, motor status, spasm and function (subjective impression). EMG	(Summary results for all outcomes reported only.) K vs D = no significant difference. K vs P = no significant difference. D vs P = no significant difference	4/5

Similarly, in the comparisons with dantrolene and tizanidine, a reduction in spasticity was observed on treatment with diazepam, but the extent of this reduction was no different to that seen with the comparator drug.

In the comparison between diazepam and ketazolam, no significant difference was reported between the two active drugs. In the larger there was a significant difference between both active drugs and placebo in the overall effect on all measured outcomes.

Preferred treatment

In both of the comparisons between diazepam and baclofen, slightly more patients favoured baclofen over diazepam than the other way round. This does not appear to have been statistically significant. In the comparison with dantrolene, 22 patients preferred dantrolene and 13 preferred diazepam.

Impact on function

No details are given of the impact of diazepam treatment on patient functioning.

Side-effects

In the comparisons with baclofen, dantrolene and tizanidine, diazepam caused significantly more side-effects than the comparator drug. The commonest reported side-effects were sedation and weakness. Four patients in each of two trials^{25,41} had to withdraw from the study because of the side-effects.

Summary

Diazepam appears to lead to a reduction in the Ashworth score, but it is no more effective than the four drugs with which it was compared, and caused significantly more side-effects.

Gabapentin (Neurontin)

Gabapentin is an anticonvulsant drug licensed for the treatment of partial seizures. It is structurally similar to the neurotransmitter γ -aminobutyric acid (GABA), but it does not bind to GABA receptors, and the mechanism of action is unknown. It is readily absorbed after oral administration, and excreted unchanged in the urine. The cost of treatment is £0.23, £0.53 and £0.61 for 100-, 300- and 400-mg capsules, respectively.²³ A typical dose of 1.2 g daily would therefore cost approximately £1.83.

Recently, the serendipitous observation that when administered to patients with MS with paroxysmal

symptoms it led to an improvement in spasticity has led to its effect on spasticity being explicitly assessed.

Quantity of research available

Four studies were identified. One was an open-label report of the effect of gabapentin on paroxysmal symptoms in MS⁴⁸ and another a report of two cases.⁴⁹ The other two were randomised, placebo-controlled, crossover studies^{50,51} of its effect on spasticity in MS. These latter two are analysed here and are summarised in *Table 15*.

Populations examined

Both studies included only patients with definite MS. One described the patients as having a 'laboratory-supported' diagnosis, the other as having chronic progressive MS. The extent of disability appears to have differed between the two studies. In one, the mean duration of disease was 8.4 years, and the median EDSS score was 12 (pre-gabapentin) or 13 (pre-placebo). [The EDSS strictly runs from 0 to 10 (death), with intervals of 0.5. It appears that the authors of this paper have reported it as running from 0 to 20, with intervals of 1.0, although this is not explicit. It is likely, therefore, that these EDSS scores ought to be halved for comparison with other quoted scores.] The other study recruited veterans (hence 20 men to two women), whose EDSS scores were 6–9. The overall age range was 31–67 years.

It is not possible to compare the degree of spasticity at baseline. In one study,⁵¹ a modified Ashworth score is used, but the way in which it has been modified is not explicit, and the results given are not interpretable in absolute terms. In the other, the median Ashworth score at baseline was 2.

Interventions

Both trials were of short duration. In one, gabapentin was administered at 400 mg three times daily for 48 hours, with an 11-day washout. In the other, the dose was 300 mg three times daily for 2 days, then 600 mg three times daily for 2 days, then 900 mg three times daily for the final 2 days, a total of 6 days of treatment altogether, with a 14-day washout. Both studies randomised patients to receive gabapentin or placebo first.

Outcomes measured

The studies assessed a variety of outcomes. These included clinical assessments (in both cases including the Ashworth score, although in one of these it had been modified in a way which was not explicit),⁵¹ subject-reported assessments and the Kurtzke EDSS.

TABLE 15 Gabapentin vs placebo

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Mueller <i>et al.</i> (1997), USA ⁵¹	DB crossover RCT	Gabapentin 400 mg t.d.s. Placebo. 48 h treatment. 11 day washout	N = 15. Laboratory-supported, definite MS. Mean age 42 y (range 31–59). Mean duration of disease 8.4 y. Median EDSS score 12 (pre-gabapentin), 13 (pre-placebo)	0	Ashworth scale (modified; details not explicit). Clinical assessment of clonus, reflexes, response to noxious stimuli. Kurtzke EDSS. Visual faces scale (pain)	Significant fall ($p = 0.007$). No change. Decrease in median score from 12 to 10 on gabapentin, from 13 to 12.5 on placebo ($p = 0.03$) ^a Decrease in median score from 2 to 1.5 on gabapentin, no change on placebo ($p = 0.008$)	4/5

continued

TABLE 15 Gabapentin vs placebo (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)	
Cutter <i>et al.</i> (2000), USA ⁵⁰	DB crossover RCT	Gabapentin 300 mg t.d.s. for 2 days, 600 mg t.d.s for 2 days, 900 mg t.d.s for 2 days. Placebo. 14 day washout	N = 22. All had chronic progressive MS. Ages 34–67 y. 20 M, 2 F. All veterans treated at Denver VAMC. Kurtzke EDSS 6–9	1 (M), after 1 day on gabapentin, due to headache	<p><i>Subject reported:</i> Spasm frequency scale. Spasm severity scale.</p> <p>Interference with function scale. Painful spasm scale.</p> <p>Global assessment.</p> <p><i>Physician reported:</i> Modified Ashworth scale. Clonus score. Deep tendon reflexes. Plantar stimulation response. Kurtzke EDSS. Digit span and digit symbol portions of the WAIS-R. Fatigue impact scale. Adjective generation technique</p>	<p><i>Effect of gabapentin vs baseline</i></p> <p>Reduced ($p = 0.0001$) Reduced ($p = 0.0004$) Reduced ($p = 0.002$) Reduced ($p = 0.002$) Reduced ($p = 0.0001$) Reduced ($p = 0.0005$) Reduced ($p = 0.002$) Reduced ($p = 0.0001$) Reduced ($p = 0.008$) Reduced^b ($p = 0.006$)</p>	<p><i>Change on gabapentin vs change on placebo</i></p> <p>Fall on G > fall on P ($p = 0.01$) Fall on G > fall on P ($p = 0.02$) Fall on G > fall on P ($p = 0.03$) Impact of G > impact of P ($p = 0.003$) Fall on G > fall on P ($p = 0.04$) Impact of G > impact of P ($p = 0.03$)</p>	4/5

^a See the comment in brackets in the section Populations examined.
^b Placebo administration also resulted in a reduction in the fatigue impact scale ($p = 0.03$) and the deep tendon reflexes ($p = 0.04$).

Validity of included studies

Both studies were of relatively high quality, scoring four out of five on the Jadad scale. Both were randomised and double blinded. Appropriate use was made of non-parametric statistics. One used a p value of 0.05 as a threshold for statistical significance, despite a multiplicity of comparisons,⁵⁰ but does quote the p values for those comparisons which it reports as statistically significant.

Summary of direction of effect

Both studies reported benefits, in terms of a reduction in spasticity, on treatment with gabapentin. The study which titrated up to the higher dose of gabapentin⁵⁰ reported a significant effect on all the physician-assessed measures of spasticity, and the other study also reported a fall in the (modified) Ashworth score (but no effect on clonus, reflexes or response to noxious stimuli). Subject-reported outcomes (spasm frequency, severity, interference with function, pain) were all also reduced in the higher dose study.

Preferred treatments

The one study which recorded an overall subject global assessment⁵⁰ reported a clear preference for gabapentin over placebo. A total of 71% of patients reported spasticity as a little or a lot better on gabapentin, compared with 24% on placebo.

Impact on function

The Kurtzke EDSS score was improved from 12 to 10 (see the comment in brackets, in the section Populations examined, above) in patients given the lower dose for 48 hours, but did not alter in the higher dose study. In that study, however, 'anecdotally, subjects reported improved activities of daily living (despite no change on the EDSS), and improved sleep, mood, and appetite'. This difference may be explained by the different baseline levels of disability.

Side-effects

Gabapentin is reported to cause fatigue and decreased concentration. The lower dose study reported 'no serious side-effects'. The other study used four different psychological measures of fatigue and concentration, and did not demonstrate any adverse impact of gabapentin. One patient, however, withdrew after 1 day on gabapentin, because of a reported headache.

Summary

These two studies provide some evidence that gabapentin is effective in alleviating clinical

measures of spasticity, at least in the short term. The longer term effect of the drug on spasticity is not established, but on the basis of these findings, warrants further investigation.

Progabide (halogabide)

Progabide is a GABA receptor agonist which was formerly available as an anticonvulsant drug. It is not currently marketed.

Quantity of research available

One DB crossover RCT was identified.⁵³ Details are given in *Table 16*.

Populations examined

Seventeen patients were included in the study, of whom 14 had MS, of between 2 and 33 years' duration. The disease was said to have been stable for at least 2 months. Five were women and nine were men.

Interventions

Progabide, at a median dose of 1800 mg per day, was given for 2 weeks, and placebo for 2 weeks in a crossover trial.

Outcomes measured

The joint angle at which a stretch reflex appears, the frequency of flexor spasms, muscle power and the global therapeutic effect as assessed by the investigator and patient were all reported as outcomes. No evidence was given that any of the scales used were validated.

Validity of included studies

The study scored four out of five on the Jadad scale.

Summary of direction of effect

The joint angle at which the stretch reflex appeared increased in 14 out of 16 patients (the results for MS patients were not reported separately), but the overall 'evaluation of the reflex response' was not altered. Flexor spasm frequency was reduced in nine out of 16 patients ($p < 0.05$). Muscle power was not affected.

Preferred treatments

Treatment was assessed as beneficial by the investigator in 87% and by patients in 81% of cases. The magnitude of the effect was judged as 'medium' or 'important' in seven cases each.

Impact on function

No details were reported on impact on function.

TABLE 16 *Progabide vs placebo*

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Mondrup and Pedersen (1984), Denmark ⁵³	DB crossover RCT	Progabide, median dose 1800 mg/day, for 2 weeks, placebo for 2 weeks	N = 17. Results reported in 16, 14 with MS, duration 2–33 y, stationary phase of disease for >2 months. 5 F, 9 M	N = 1, on placebo, due to urinary tract infection	Measurement of joint angle at which stretch reflex appears, and duration of response. Evaluation of reflex responses. Frequency of flexor spasms. Flexor reflex of lower limbs. Voluntary muscle power. Global therapeutic effect assessed by investigator and patient	Angle at which stretch reflex appeared increased in 14/16 patients. Not significantly altered. Reduced in 9/16 (<i>p</i> < 0.05). Not significantly altered. Not significantly altered. Assessed as beneficial by investigator in 87% and by patient in 81% of cases. Magnitude of effect judged as 'medium' or 'important' in 7 cases each. No side-effects registered	4/5

Side-effects

No side-effects were reported.

Summary

This single trial suggested that progabide may have an antispastic effect in patients with MS. However the study was small, of short duration and did not report on functional outcomes. At best it can be taken as an indicator that more research is needed.

BT (Botox, Dysport)

BT A is one of seven neurotoxins produced by the bacterium *Clostridium botulinum*. It causes the clinical syndrome of botulism, a progressive flaccid paralysis, following ingestion of the toxin. Paralysis is caused through preventing the release of acetylcholine from nerve endings, thus causing a presynaptic neuromuscular block. Injection of very small doses of the toxin produces local paralysis, and individual muscles can, therefore, be weakened. The duration and extent of the paralysis depend on the dose administered.

BT is licensed for the treatment of blepharospasm, spasmodic torticollis and hemifacial spasm in adults, and dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients. It is not currently licensed for treatment of spasticity in MS in the UK.

The cost of one vial of Botox (100 units) is £128.93 and that of Dysport (500 units) is £164.74.²³ Trials have used between 50 and 400 units. The cost of treatment would also include the cost of disposables (needles, syringes, etc.) and the time of the clinician who administers the injection(s). The units employed for the two brands are not interchangeable and are not equivalent. The total dosage of Botox should be no more than 200 units and no more than 50 units at one site. The initial recommended dosage of Dysport is 500 units per patient in total. Depending on the clinical response, the dosage of Dysport can range from 250 to 1000 units. It should be noted that BT therapy would normally be carried out in conjunction with a regime of physiotherapy which would add to the total cost of treatment. A single treatment of BT should last for between 6 and 12 weeks. If one assumes an average duration of a single treatment to be 8 weeks, then the cost of treating two muscle sites with Botox would be £2.30 per day. This excludes other costs such as the syringe and physiotherapy.

Quantity of research available

Twelve papers were identified, of which two were reviews. Of the remaining 10 studies, only five were retained for this review. One was excluded because, although the study was on the treatment of spasticity, it did not include patients with MS,⁵⁴ and the other four were discarded because they were either single case studies or a report of two cases only.

Details of the five papers selected for inclusion in this review are given in *Table 17*. Of the five included, two were open-label studies of patients administered the treatment, with longitudinal follow-up.^{55,56} One of these was primarily concerned with documenting the role of EMG in determining the suitability of muscles for treatment and monitoring toxin effect.⁵⁵ The other three were DB placebo-controlled crossover RCTs, two of which recruited exclusively MS patients whereas the other did not. In one study, the second treatment was administered 3 months after the first,⁵⁷ whereas in another, the second treatment was administered 2 weeks after the first, or when any clinical effect of the first had worn off. This indicates that clinical effects were obvious, which calls into question the effectiveness of the blinding (to both patient and physician).

Populations examined

All patients in the selected studies had chronic or severe spasticity and in many cases were non-ambulant. Two studies recruited only patients with MS. One recruited nine women, one man, mean age 40 years, from long-stay institutions, none of whom were ambulant, and whose mean disease duration was 18 years.⁵⁷ The other recruited 74 patients (46 women, 28 men), with disease of 16–23 years' duration.⁵⁸ The other studies were not restricted to MS patients. No information is given about functional status, except for the two patients in the case reports.⁵⁹ In one of these the main problem arising from the spasticity is said to have been scissoring, which interfered with walking between parallel bars. In the other, the main problem was flexor spasms.

Intervention

BT was administered intramuscularly. One RCT used a total of 400 mouse units (10 units = 4 ng) in three different muscle groups.⁵⁷ (One mouse unit is the median lethal intraperitoneal dose for mice.) A second RCT used 25–250 units of Botox (titrated according to muscle bulk).⁶⁰ The third RCT was a dose-ranging study, using doses of 500, 1000 or 1500 units of Dysport to treat both legs simultaneously on a single occasion.⁵⁸ The other

TABLE 17 BT studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Snow <i>et al.</i> (1990), Canada ⁵⁷	DB placebo-controlled crossover RCT	BT (non-commercial preparation). 160 ng (400 units) administered intramuscularly in 3 muscle groups. 6 weeks	N = 10. Mean age 40 y (23–61). 9 F, 1 M. All had stable MS with a mean duration of 18 y. Non-ambulant. Recruited from long-stay institutions	N = 1, on placebo	Scale adapted from the Ashworth scale. Spasm frequency score. Hygiene score	BT showed significant reduction in spasticity over placebo ($p = 0.009$). Frequency score in treatment group decreased from mean 2.9 to 2.7, but this was not significant. Statistically significant improvement in treatment group in hygiene score ($p = 0.009$). No change in placebo group. The greatest benefit was found in the most severely affected patients. No adverse effects were noted	5/5
Grazko <i>et al.</i> (1995), USA ⁶⁰	DB placebo-controlled crossover RCT	BT (Botox). 25–250 units. Placebo. Treatment 2 given 2 weeks after treatment 1, or when any clinical effect had worn off	Total N = 20, of whom 12 had spasticity, and of these 5 had MS. Basis of diagnosis not stated. 3 F, 2 M. Ages 40–66 y. Baseline Ashworth score 3–4+	N = 0	Modified Ashworth scale	Reduction of at least two grades on the Ashworth score in all five patients with MS, lasting 1–3 months. 'Subjective improvements in movement and posture'	3/5

continued

TABLE 17 BT studies (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Cava (1995), USA ⁵⁶	Open trial. Patients were followed up every 2 weeks, but the total duration of the study is not clear. The duration of effect was found to be 3–6 months	BT (Botox). Intramuscular dose per muscle varied from 40 to 180 units. Maximum dose range 270–300 units	N = 16, 10 of whom had MS (MS patients who had taken corticosteroids in previous 6 months excluded). All aged > 18 y. All had dysfunctional limb spasticity but no details of functional status	N = 0	Modified Ashworth scale. Frequency of spasm scale. Pain scale	13/16 patients (8/10 MS patients) showed significant improvements. There was no change in 3 patients (2/3 were MS patients). Mean Ashworth score changed from 2.6 to 1.3. This change was statistically significant. Tone improved 2–6 weeks after treatment. Spasm frequency also declined but it was not statistically significant. There was a large reduction in pain particularly in the MS patients. Adverse effects were minimal, mainly temporary bruising	0/5

continued

TABLE 17 BT studies (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Finsterer <i>et al.</i> (1997), Austria ⁵⁵	Prospective, open-label, uncontrolled longitudinal with follow-up after 17–57 days after initial injection	BT (Dysport). Mean intramuscular dose per patient 276 units. Mean dose per muscle 116 units. 3 of the patients had a booster dose owing to lack of response initially. The number of muscles treated was between one and five. Muscles were selected for injection if their TAA > 150 ^a	N = 9. Mean age of MS patients = 52 y. 4 F and 1 M. 5 had severe spasticity, 3 had right upper or lower limb spasticity and 1 had tetraspasticity. The spasticity was due to MS in 5 cases. The average duration of spasticity in MS cases was 16 y	N = 0	TAA (EMG measure) ADL. Pain. Muscle tone (Ashworth scale). Range of motion	All outcome measures were assessed on a 5-point scale by the doctor, not the patient. The duration of follow-up varied. There is no evidence that this scoring system has any validity. All 5 MS patients showed an improvement in TAA, mostly by at least 2 points. 4/5 MS patients showed an improvement of 1 point. 4/5 patients showed an improvement in pain. 3/5 MS patients showed an improvement. 3/4 MS patients showed an improvement. Scores for all patients improved at a statistically significant level. Improvement did not appear to be dose dependent. The injection was tolerated by all patients without complaint and there were no major side-effects	0/5

continued

TABLE 17 BT studies (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Hyman <i>et al.</i> (2000), UK ⁵⁸	DB placebo-controlled, dose-ranging RCT	BT (Dysport) 500 (<i>n</i> = 21), 1000 (<i>n</i> = 20), 1500 (<i>n</i> = 17) units or placebo (<i>n</i> = 16). Single treatment (both legs) only	<i>N</i> = 74. All with probable or definite MS, with disabling spasticity of hip adductors, Kurtzke Expanded Disability Status (KEDS) ≥ 7, stable for 6 months, moderate pain or difficulty in nursing, hygiene score ≥ 2. 46 F, 28 M. Mean duration of MS 16–23 y. Mean ages 47–54 y. Concomitant medication continued	<i>N</i> = 2 prior to week 4, <i>N</i> = 14 prior to end of study at week 12, due to need for retreatment	Angles of active and passive hip abduction. Maximum distance between knees on passive hip abduction. Modified Ashworth score (muscle tone × spasm frequency). Upper leg pain (4-point scale). Clinical global rating (4-point scale). Perineal hygiene score (6-point scale). Overall investigator and patient rating. Time to retreatment. Primary analysis was performed on the change from baseline at week 4	Passive abduction increased in all groups, no difference between groups. Statistically greater increase in 1500-U group than in placebo (<i>p</i> = 0.02). Improved in all groups, no difference between groups, although in placebo group, unlike the treated groups, the improvement was due to a reduction in spasm frequency only, with no reduction in tone. Proportion pain free increased in all groups, no difference between groups. Median rating improved from severe to moderate in all groups. Median score unchanged in placebo and 500-U groups, improved from 2 (one person able to clean/catheterise with effort) to 1 (the same, with ease) in 1000- and 1500-U groups. Similar in all groups. Median time to retreatment 56, 99, 111, 119 days in placebo (<i>n</i> = 7), 500-U (<i>n</i> = 8), 1000-U (<i>n</i> = 10), 1500-U (<i>n</i> = 9) groups, respectively (<i>p</i> = 0.015). Adverse events reported in 55% of patients on active treatment, 63% on placebo	5/5

^a TAA, turn/amplitude analysis.

studies used between 50 and 400 units of each preparation. The RCTs used a single dose only, whilst in the other studies some patients received booster injections.

Outcomes

All three RCTs used the Ashworth scale, either as a direct measure of spasticity⁶⁰ or combining the Ashworth score (muscle tone) with a score of spasm frequency.^{57,58} One measured the angle of active and passive hip abduction and the maximum distance between the knees on passive abduction.⁵⁸ Two measured a hygiene score.^{57,58} One measured in addition a 'clinical global rating', overall investigator and patient rating, and the time to retreatment.⁵⁸

One of the case series⁵⁶ also reported on the modified Ashworth scale and spasm frequency. The other case series⁵⁵ used a specifically designed efficacy score, which incorporated activities of daily living, pain, tone, passive range of motion and turn/amplitude analysis count (an EMG measure of muscle activity).

Validity

One of the RCTs which recruited exclusively MS patients appears to have been conducted in an exemplary fashion and, therefore, to be robust, except that the authors appear to have used their own adapted version of the Ashworth scale.⁵⁷ Appropriate sample size calculations had been undertaken. The evaluations were undertaken 'blind' by two separate neurologists, with a high degree of correlation between them (correlation coefficient 0.93 for spasticity score, 0.81 for hygiene score). However, there is no evidence to support the validity of the scales used. The researchers claim to have based their assessment of the degree of muscle tone on the Ashworth scale, but the categories used in the study bear no relationship to published versions of the scale.

The second RCT which recruited only MS patients also scored 5/5 on the Jadad scale. Unfortunately, there again is no evidence for the validity of the rating scales used. That study was unable to recruit the 80 patients required to gain 90% power to detect a difference at the 5% level, and was calculated to have only an 80% power.

In the other RCT the blinding is questionable, which may have led to bias in reporting.

The validity of the other studies, being neither randomised nor blinded, and of limited sample size, must be questionable. However, the use of

small, open-label trials with this condition and intervention is understandable. Because relatively little evidence is available, their findings are reported here.

Finsterer and colleagues⁵⁵ claimed to be using the modified Ashworth scale, but were in fact using the earlier shorter version of the scale.⁶¹

Spasticity specific outcomes

In the RCTs, there was a significant reduction in spasticity scores following treatment with BT, which was not seen following placebo injection. In one of the MS-only studies, the main contribution to the decline in spasticity score was the decrease in muscle tone (quoted as a decrease of 2.6 on a five-point scale, but as it is a non-continuous scale the appropriateness of this figure is questionable). There was no statistically significant decrease in spasm frequency. There was no evidence of any carryover effect.⁵⁷ In the second MS-only study,⁵⁸ spasticity, as measured by the product of muscle tone and spasm frequency improved in all groups (including those treated with placebo), but in the placebo-treated group this was due to a reduction in spasm frequency only, not a reduction in muscle tone. This study claims that there is a reduction in hip adductor spasticity on treatment, although the only significant changes observed were an increase in the maximum distance between the knees on passive abduction and an increased time to retreatment in treated rather than placebo groups. There does appear to have been a dose-response effect.

In the case series, muscle tone was also observed to fall (in eight of 10 MS patients in one study,⁵⁶ and three of five in the other⁵⁵), with a maximum effect at 2–6 weeks post-treatment.

Preferred treatment

None of the studies reported patient preference.

Impact on function

In one of the MS-only RCTs, there was a statistically significant improvement in hygiene score following BT treatment (400 units), which was not seen following placebo. The greatest clinical benefits occurred in patients with the highest initial scores. In two patients, one nurse was able to perform care that had previously required two. In another, a chronic perineal excoriation became accessible to treatment and healed. However, in four of the nine patients the change in hygiene score was negligible or nil.⁵⁷ In the second MS-only RCT, hygiene improved in the two groups of patients administered the higher

doses (1000 or 1500 units), but not on placebo or the lower dose (500 units).⁵⁸ The validity of the hygiene score is questionable. In the other RCT, there were 'subjective improvements in movement and posture'.

In the case series which reported specifically on the effect on activities of daily living (ADL), four out of five MS patients were said to have had an improved ADL score.⁵⁵ The other case series, and the case reports, also reported significant functional improvement.

Side-effects

One of the RCTs reported adverse events in 55% of patients on active treatment, compared with 63% of patients on placebo.⁵⁸ The only other side-effects reported were bruising of the injection site in three patients in one of the case series.⁵⁶ This resolved within 24 hours. The potential for overweakening muscles with high doses is noted. Interestingly, the RCT which was not restricted to MS patients, and which used a slightly lower dose, reported that there was 'no significant muscle weakness', which the authors attributed to titration of dose against muscle bulk.

Summary

Although BT is not licensed in the UK for the treatment of spasticity in MS, there is evidence that it is effective. Because it has its effects through causing paralysis, its role is restricted to those cases in whom the relief of spasticity is of greater functional benefit than retaining any muscle strength. In practice, this is likely to be only the most severely disabled patients. Much of the benefit will come from allowing more effective carer support.

Intrathecal baclofen

The site of the antispastic effect of baclofen (see above) is the spinal cord. As the drug has poor lipid solubility, it does not cross the blood-brain barrier well, so relatively low concentrations are found in the cerebrospinal fluid (CSF) in response to an oral dose (unfortunately, it does cross into the cerebral CSF in sufficient quantities to cause side-effects). The administration of baclofen directly into the spinal canal through a programmable infusion pump allows a continuous supply of drug to the site of action while potentially avoiding side-effects. Costs, which include the cost of the drug together with the cost of administration, are referred to in the review of economic evidence below.

Quantity of research available

Twenty studies evaluating the use of intrathecal baclofen were identified. Five were excluded because the number of patients with MS was less than 50% of the total and the results for this group of patients were not presented separately. Fifteen studies are included in this review, details of which are summarised in *Table 18*. Four studies⁶²⁻⁶⁵ come from the same centre, and it is not clear to what extent the patients were included in more than one of them.

Of these, one⁶⁶ was a DB RCT lasting 13 weeks. Another was a short-term (3 days) crossover RCT,⁶³ whilst another study⁶⁷ used a DB randomised technique in the initial screening to assess initial response to a bolus dose before recruiting subjects into the open-label, uncontrolled studies. The remaining 12 studies were longitudinal, open-label, uncontrolled designs or case series.

It is unfortunate, but understandable, given the complex nature of this intervention, that there was only one longer term DB RCT. Researchers may be either unable or unwilling to randomise or blind subjects. Many factors militate against the use of a DB RCT design for this treatment in patients with MS, including the invasive nature of the intervention, possible ethical objections, the need to titrate dosage over time and the large number of treatment-related complications.

Despite the obvious potential for bias arising from the design of the other studies, they have been included in this review because of the lack of other evidence. The duration of treatment in the studies ranged from 4 months to 6 years.

Populations examined

None of the studies was restricted to patients with MS. However, in all included studies 50% or more of the subjects had MS, or the results for the MS patients were shown separately. In all 15 studies all patients had severe spasticity and in six studies the subjects were stated explicitly to be unresponsive to oral therapy. In most of the studies the subjects were non-ambulatory and most had had their condition for a long time.

The populations studied in these papers can be regarded as broadly similar.

Intervention

All studies examined the effect of baclofen administered intrathecally by programmable continuous infusion pump. Most of the studies

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Saltuari <i>et al.</i> (1992), Austria, Italy ⁷²	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. Mean final dose for MS patients 239 µg/day. Treatment duration 2–24 months	N = 11, of whom 6 had MS. Ages 30–57 y. 5 F, 1 M. Disease duration 6–27 y	None documented	Ashworth scale. Reflexes assessed on a six-point scale. Physician and physiotherapist assessment of motor performance	Results in MS patients not reported separately. Mean Ashworth score for Knee flexion reduced from 3.4 to 1.25, for knee extension from 3.4 to 1.4. Patellar reflex score reduced from ~3.9 to ~1.4. One MS patient reported to be able to use staircase. 4 catheter dislocations, one catheter break, one catheter torsion	N/A
Becker <i>et al.</i> (1995), Canada ⁶⁸	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. Mean dose at follow-up for MS patients 542 µg/day. Treatment duration 13–34 months	N = 9, of whom 6 had MS. Ages 34–56 y. 4 F, 2 M. All were non-ambulatory and many could not sit properly owing to their severe spasticity. The MS patients were all severely disabled, with little or no leg function and marked arm weakness. 6/9 were unable to live at home. Average duration of MS 16.5 y	None documented	Nursing assessment of transfers, pain control, nursing care and skin breakdown. Self-reported satisfaction survey of MS patients (1–5 score). Place of residence. No. of days in hospital	There were major improvements in transfers (5/6), pain control (4/6), nursing care (5/6) and skin breakdown (5/6). All items showed major improvements, in particular, the ability to transfer, seating ability, personal hygiene, sleeping ability and pain control. 3 out of the 6 MS patients who were previously hospitalised were able to be discharged. The average time spent in hospital reduced from 108 to 28 days per year. There were a number of significant complications, including: surgical catheter revisions, pseudomeningocele repair and problems with pump refills	N/A

continued

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Broggi <i>et al.</i> (1993), Italy ⁶⁹	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. Mean dosage in MS patients 178 mg/day. Mean duration of treatment 9 months	N = 12, of whom 4 had MS. 2 F, 2 M. Mean age 50 y. Mean duration of disease 16 y. Unresponsive to oral therapy. Mean Ashworth score 3.8. All MS patients were bedridden	None	Ashworth scale. Frequency of spasm scale	Mean score before treatment was 3.8; this fell to 1.8 after treatment. Muscle spasms were abolished. No reported side-effects in MS patients. There were pump-related complications in other patients	N/A
Penn <i>et al.</i> (1989), USA ⁶³	DB crossover RCT	Intrathecal baclofen. 100–150 µg/day or saline administered for 3 days in randomised crossover trial. Long-term follow-up for mean of 19 months (mean dose 223 µg/day)	N = 20, of whom 10 had MS. Ages 31–62 y. 7 F, 3 M. One MS patient able to walk a short distance with crutches, the rest wheelchair bound. Mean Ashworth score 4.0	None	Ashworth scale, spasm frequency (0–4), laboratory analysis of motor control, neurological examination by neurosurgeon, patient assessment of 'on' and 'off' periods	In MS patients: No explicit results given for the short-term crossover trial, but period of baclofen infusion said to have been correctly identified by each assessment. In long-term follow-up, mean Ashworth score decreased from 4.01 to 1.05, mean spasm score decreased from 2.9 to 0.2. Of 20 patients, in 26 months follow-up, 2 catheters dislodged, one pump failure, one painful implant site	3/5
Parke <i>et al.</i> (1989), USA ⁶⁴	Long-term follow-up	Intrathecal baclofen. 67–550 µg/day. 3 and 6 months follow-up	N = 8, of whom 4 had MS. May be same patients as included in other studies from the same centre ^{62,63}	None	Ashworth scale. Functional outcomes using PECS (Patient Evaluation Conference System) scale	Ashworth score reduced from 4 or 5 to 1 in all 4 MS patients. Bladder care score improved in all 4 patients (indwelling urinary catheter removed in one patient), dressing skills improved in 2 of 4 patients	N/A

continued

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Penn (1992), USA ⁶⁵	Case series	Intrathecal baclofen. Mean initial dose 200 µg/day	N = 66, of whom 33 had MS. Presumably some of the same patients as included in other studies from the same centre ⁶²⁻⁶⁴	N = 2, because they needed extension rigidity for standing	Ashworth scale. Spasm scale (0-4)	For all patients: Pre-implantation mean score ~3.7 falling to ~1.4 after implantation, maintained for up to 81 months. Pre-implantation mean score ~2.9 falling to ~0.8 after implantation, maintained for up to 81 months. Complications: 1 meningitis, 1 pocket infection, 19 fungal infection of pumps (no clinical impact, all replaced), 9 pump failures out of 91 pumps, 25 catheter complications (various), 5 procedural complications. Complications of baclofen: drowsiness (22), dizziness(10), blurred vision (10), slurred speech (6)	N/A
Broseta et al. (1989), Spain ⁷³	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. 60-172 µg/day. Mean follow-up 5 months	N = 8, of whom 4 had MS. Ages 27-54 y. 3 F, 1 M. All had severe spasticity and were unresponsive to oral treatments. Ashworth score 2-4. 4 cases were either in a wheelchair or bedbound	None	Ashworth scale. Frequency of spasm score. Functional assessment	All patients showed a reduction of at least one point on the scale. All patients showed a reduction in frequency of spasms. All 4 cases had increased walking ability, transfers and daily activity. The non-ambulatory patients gained only in QoL and comfort	N/A

continued

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Coffey <i>et al.</i> (1993), USA ⁶⁷	Screening protocol was a DB RCT, followed by open-label longitudinal study	Intrathecal baclofen. Mean starting dose 171 µg/day. Mean dose at follow-up 320 µg/day. Placebo. Patients followed-up after a mean of 19 months (5–41 months)	N = 93 patients screened, of whom 31 had MS. 75 patients had a pump implanted, of whom 27 had MS. 53 of the 75 were male. Average age 42 y. All had severe chronic spasticity and were refractory to oral drugs	N = 1, due to late surgical complication (pump pocket infection)	Ashworth scale (adapted slightly). Frequency of spasm score (0–5)	Mean score for MS patients with intrathecal baclofen decreased from 2.9 to 1.6. Mean score for MS patients reduced from 2.7 to 0.7. One patient received an overdose due to human error. 3 mechanical failures, 6 wound complications, 22 catheter complications out of the 75 implantations	0/5
Dressnandt <i>et al.</i> (1995), Germany ⁷⁴	Prospective, longitudinal, uncontrolled	Intrathecal baclofen for mean of 61 months. At end of 1st year, mean dose was 189 µg/day	N = 27, of whom 20 had MS. Ages 38–66 y. 16 F, 4 M. Average age of MS patients was 52 y. All with severe paraspasticity or tetraspasticity	None documented	Ashworth scale. Frequency of spasm scale	Decreased in all 20 MS patients. Decreased in all 20 MS patients. (N.B. The primary outcome reported in this trial was the ability to withdraw intrathecal baclofen after prolonged treatment. This was reported to be possible in 5 MS patients)	N/A

continued

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Gianino <i>et al.</i> (1998), USA ⁷⁵	Prospective, longitudinal, uncontrolled	Intrathecal baclofen (Synchromed). Mean dose at 12 months 298 µg per day	N = 25, of whom 15 had MS. All had intractable spasticity of spinal origin. Most were paraparetic, 6 were quadriparetic, 1 hemiparetic and 1 monoparetic. Mean age 39 y. 15 F, 10 M	N = 9. No reasons given other than questionnaire fatigue	Ferraris and Powers QoL Index. SIP (0–100 scale). Ashworth scale. Frequency of spasm score	No change between baseline and 2 months. It was felt that this lack of change was due to the emphasis of the QoL on non-physical aspects. SIP improved from 29.7 to 21.7 (<i>p</i> = 0.8) Physical sub-score went from 38.5 to 31 (<i>p</i> = 0.001) Psychological subscore went from 20.8 to 13 (<i>p</i> = 0.025) Significant decrease from 3.8 to 1.5 (<i>p</i> value not stated). Significant decrease from 2.6 to 0.5 (<i>p</i> = 0.00001)	N/A
Lazorthes <i>et al.</i> (1990), France ⁷⁰	Prospective, longitudinal, uncontrolled. The mean follow-up period was 18 months (range 4–43 months)	Intrathecal baclofen. Individual doses in MS patients ranged from 100 to 250 µg per day	N = 18, of whom 6 had MS. MS patients ages 40–56 y. 5 F, 1 M. All patients had severe, debilitating spasticity and were unresponsive to oral treatment	None	Ashworth scale. Modified Davis and Gray scale for the evaluation of motor performance. Painful muscular spasms. Functional assessment	2–4 point improvement in all 6 patients. 1/6: large improvement 1/6: moderate improvement 4/6: no improvement in function. Abolition of painful spasms in 5/6. Significant functional improvement was noted in 1 MS patient. Functional improvement was much greater in those with traumatic lesions as opposed to those with MS. Two MS patients had serious complications (overdose, meningitis)	N/A

continued

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Middel <i>et al.</i> (1997), The Netherlands ⁶⁶ The cost analysis of this study is covered in the paper by Postma <i>et al.</i> (see Table 21)	DB RCT for 13 weeks, followed by a longitudinal observational study for 52 weeks	Intrathecal baclofen. 75–150 µg per day Placebo	N = 22, of whom 12 had MS. Aged 19–70 y. 55% women (all patients). Baclofen N = 12. Placebo N = 10. All 22 received intrathecal baclofen in the observational study. All patients had chronic, disabling spasticity and were not responding to oral medication	None	Ashworth scale (claims to be modified version but is standard version). Frequency of spasm score. Self-reported pain. QoL measured by the SIP. Hopkins symptoms checklist (HSCL)	Significantly greater fall in Ashworth, spasm and pain scores in treated cf. placebo groups at 3 months. Effect sizes 0.2, 1.4 and 0.94, $p < 0.05$, <0.01 , <0.05 , respectively. No significant differences in change in SIP or HSCL. Significant fall in Ashworth, spasm and pain score on treatment at 3 (not for pain) and 12 months Significant improvement in SIP, HSCL on treatment at 3 and 12 months	5/5
Ochs and Tonn (1996), Germany ⁷⁶	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. Mean dose 199 µg/day at 1 year. Study duration up to 5 years	N = 70, of whom 59 had MS. Ages 35–69 y. Sexes not stated. All patients suffered from spinal lesions resulting in severe spasticity. Mean Ashworth score 4.1	N = 2, both with MS. Two MS patients died during the study, but this was thought to be unrelated to their treatment	Ashworth scale. Spasm score. Changes in mobility. Subjective evaluation	Significant reduction in muscle tone at on average 2 points below the initial baseline score. This reduction was sustained over 5 years in 12 patients. Spontaneous spasms also reduced but less reliably than muscle tone. At baseline 54% (38/70) were bedridden. After 6 months 22 of the 38 could leave bed and use a wheelchair. Initially, 14 patients were wheelchair bound. After treatment 4 of these were able to stand. After 6 months 19/22 patients and 20/22 physicians rated the outcome as good or excellent	N/A

continued

TABLE 18 Intrathecal baclofen studies

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results (MS patients only)	Trial quality (Jadad)
Patterson <i>et al.</i> (1994), UK ⁷¹	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. Initial mean dose 223 µg/day. Effective mean dose 485 µg/day. Treatment duration varied from 9 to 79 months	N = 21, of whom 15 had MS. Mean age 46 y (range 24–67). Sexes not stated. All patients had severe spasticity and were unresponsive to oral treatment. None was ambulant	7 patients died but this was thought to be unrelated to the treatment. Complications in 9 patients led to the pump being removed. This included infections leading to meningitis in 5 patients	Ashworth scale. Frequency of spasm score. Barthel index	'Complete and sustained' fall in score in 16/21 patients. In 4 other patients there was short-term benefit. 18/21 patients showed a complete absence of spasms. 15/15 MS patients showed a complete absence of spasms. No change in any patients, possibly due to inappropriateness of this measure. 16/21 patients showed sustained improvements but the 2 patients who showed the greatest improvements in terms of mobility and ability to drive did not have MS	N/A
Penn and Kroin (1985), USA ⁶²	Prospective, longitudinal, uncontrolled	Intrathecal baclofen. Initially 12–200, later 12–400 µg/day for 7 months	N = 6. 3 with MS. All had severe rigidity in lower limbs (Ashworth score 4–5) and 5/6 had frequent spasms. 5/6 non-mobile, 1/6 partially mobile. All female, with an average age of 36 y (range 19–54)	N = 1	Ashworth scale	All patients showed an immediate and long-lasting return from a score of 4–5 to 1 (normal tone). Spasms were controlled in all patients and stretch reflexes were reduced in half. None of the patients had any of the central side-effects which they had with oral baclofen. Functional improvement in ADL reported	N/A

involved an initial screening stage, in which baclofen was administered as a bolus dose to test the responsiveness of the patient. If this was successful, a pump and catheter were then inserted for the administration of the baclofen on a long-term basis. The long-term dosage used in these selected studies ranged from 21 to 648 µg per day.

Outcomes measured

A number of different outcome measures were employed, the main ones being the Ashworth scale and various spasm frequency scales. Other miscellaneous outcome measures such as Ferrars and Powers Quality of Life Index and the Sickness Impact Profile (SIP) were also used.

Validity of included studies

Only three studies were DB RCTs and, of these, only one was a longer term study, which scored 5/5 on the Jadad scale. However, despite the weaker methodological design of some of the other studies, there is a need to include these in the review for the reasons given above. Most of these studies are uncontrolled and open-label, for which a Jadad score is inappropriate. It is important to be aware of the inherent biases produced by studies of this design.

In unblinded assessments, subjective outcome measures are more likely to be reported as having been affected by the intervention than objective measures. Therefore, it is possible to attach more credence to some outcome measures than others. For example, a change in status from wheelchair bound to an ability to stand may have more credence than a change in the Ashworth score.

The longitudinal studies and case series relied on the observation of the patients' condition prior to implantation of the pumps as controls against which to assess the impact of the intervention. This is not ideal, as it does not allow for any change in the condition of the patients, which could have occurred spontaneously. However, although MS can be a relapsing and remitting disease, it appears that in the majority of these cases the disease was stable, so that one can be reasonably confident that the condition of the patient would not have altered significantly without the intervention.

It is also important to consider sample size. The sample sizes of the 11 studies ranged from 6 to 93, with many at the lower end. Some of the studies may not have had adequate levels of statistical power and most did not attempt to justify their sample size.

Generally, there was an absence of data analysis using statistics in the included studies, with many of the studies resorting to just describing the findings.

Effect on spasticity

The selected studies show an overall positive outcome for patients treated with intrathecal baclofen. All 15 trials reported positive findings. In those that reported the Ashworth score, it fell almost universally by 2–3 points, typically from 3–4 pre-implantation to 1 on treatment. Similarly, there was a near-universal abolition of spasms, which was reflected in spasm frequency scores.

Impact on function

Becker and colleagues⁶⁸ attempted to measure various aspects of nursing need, such as ease of transfer, pain control, nursing care and skin breakdown, in addition to assessing patient satisfaction. In both cases the study found major improvements. Five studies attempted to measure functional ability. Broggi and colleagues⁶⁹ found that the less severe cases gained the greatest improvements in terms of mobility and daily activity. The non-ambulatory patients gained only in terms of QoL and comfort. Lazorthes and colleagues⁷⁰ reported similar findings. On the other hand, Patterson and colleagues⁷¹ found no change in the Barthel index, despite substantial improvements in the Ashworth and spasm scores.

Complications and side-effects

Complications are not infrequent, relating primarily to problems with the pump and catheter. In particular, kinking and dislodging of the catheter and breaks in the catheter are not infrequent. Pump failure, particularly with earlier models, is also reported. In contrast, side-effects from the drug itself are uncommon, with the most commonly reported being drowsiness, dizziness, blurred vision and slurred speech. Erectile dysfunction is also reported in one patient.⁷² Acute accidental overdose as a result of pump malfunction⁶⁵ and human error⁶⁷ is also reported. One of these resulted in coma, from which the patient recovered.

Summary of systematic review of intrathecal baclofen

The studies indicate that patients with severe spasticity are likely to benefit from treatment with intrathecal baclofen in terms of a reduction in spasticity, improved ability to sit in a wheelchair, possibly to stand and improved nursing care. Patients with less severe disability may also benefit

from improvements in care with ability to transfer and painful spasms being likely to be reduced considerably. There is some evidence that bedridden patients with very severe forms of MS are unlikely to benefit in terms of improved functionality or mobility but may benefit from generally improved care and hygiene. In spite of the weaknesses of the study designs, one can conclude from the striking benefits seen in these studies that intrathecal baclofen has a positive outcome for MS patients with severe spasticity.

Phenol

Phenol injection into or around a nerve produces a temporary block that may last for months. It has been used as a neurolytic agent for over 60 years. Initially it was used to produce a sympathectomy in the treatment of peripheral vascular disease. Subsequently it has been used to treat intractable cancer pain and to control muscle spasticity. This may be achieved either through injection at the level of the spinal cord, or at the level of a peripheral nerve, or at the motor end plate.⁷⁷ Aqueous 5% phenol is produced in ampoules in packs of 10 for a cost of £21.30. A single ampoule containing 5 ml of phenol would therefore cost £2.13. As the duration of the effect is not clear, it has not been possible to calculate a cost per day. There would also be a moderate cost of disposables and clinician time associated with its use.

Quantity of research available and study characteristics

We were not able to identify any controlled studies of the effect of phenol injection on spasticity, either in MS or when due to other causes. One controlled study was identified which compared the effect of two different approaches to obturator nerve block in patients with adductor spasticity (30% of whom had MS),⁷⁸ but this was small, and used (apparently) unvalidated outcome scales. Its greatest value is probably therefore as a case series documenting the effect of obturator blockade, irrespective of approach used. Four other case series were identified which included patients with MS (although sometimes the number with MS was not specified). Because of the lack of higher grade evidence, the study inclusion criteria have been relaxed to include these. Details of the studies included are given in *Table 19*.

Populations examined

Few details are given about the patients included in the studies, or how they were selected, other

than that they suffered from spasticity, with the exception of one report of two cases of patients with painful spasms due to longstanding MS.⁷⁹ Two of the case series do include case examples,^{80,81} but there is no indication that these are typical of all the cases.

Outcome measures

The case series all simply reported the overall effect of the injection in general terms. The comparative study of the two different approaches to obturator block used what appear to be *ad hoc* scales for spasticity, hygiene and gait, in addition to reporting overall success rate and patient acceptability.

Validity and generalisability

The validity of the observations made in uncontrolled case series can always be called into question because of the lack of information about the condition the patients would have been in without treatment. Nevertheless, where natural history of a condition is that it is stable or steadily deteriorating, and intervention is followed by a prompt improvement in the condition, we can take it that this is likely to be due to the intervention. The one controlled study was small, used *ad hoc* outcome scales for which no evidence of validity was cited and did not include any discussion of sample size. Conclusions with regard to the differences between the two groups (two different approaches to obturator block) can therefore only at best be seen as tentative.

Although we may assume that the observations in the case series are valid, there is insufficient information about patient characteristics and selection to enable judgement to be made about the generalisability of the results.

Summary of the direction of effect and impact on function

All of these case series reported relief of spasticity in a high proportion of cases. In the one study which used more explicit outcome measures⁷⁸ there appears to have been a marked reduction in adductor spasticity, improved hygiene and improved gait. In the case series of two,⁷⁹ one patient was rendered able to sit in a wheelchair (previously unable to) with improved hygiene, while the other was also enabled to sit in a wheelchair, albeit only for 1–2 hours at a time. One case example is cited of a woman who was able to resume sexual relationships after obturator blockade.⁸¹

TABLE 19 Phenol

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Cain (1965), USA ⁸⁰	Case series	Phenol in glycerine solution. Variable concentration, 3–10%. Dose 0.5–0.6 ml. Subarachnoid injection	43 patients treated overall, of whom 8 had MS. 33 were treated for spasticity, 19 for pain	None	Observed relief of spasticity	Of the 33 patients treated for spasticity, 28 (85%) said to have had good or excellent relief	Not applicable
Copp <i>et al.</i> (1970), UK ⁸²	Case series	Phenol in aqueous solution: 3% for nerve blocks, 5% for motor point blocks. Volume 1–4 ml. Injection site located using nerve stimulator	50 blocks performed on 33 patients including an unspecified number with MS	None	Observed relief of spasticity	'A useful reduction of spasticity for up to 13 months'	Not applicable
Awad (1972), USA ⁸¹	Case series	Phenol in aqueous solution, 5%. Volume 0.1–0.2 ml. Obturator or lumbar plexus block	Obturator blocks: 56 patients, 28 with MS. Lumbar plexus block: 13 patients, 5 with MS	None	Observed relief of spasticity	Not explicitly stated, though effects reported to last from 3 to 14 months (slightly longer for lumbar blocks). Overall reported to lead to improved gait, transfer, dressing, hygiene, bladder and general nursing care	Not applicable
Browne and Catton (1975), Canada ⁷⁹	Two cases	Phenol in glycerine: 1 ml 10% in one case; 1.5 ml 5%, followed by 1.5 ml 20%, then 2 ml 20%, in the other. Intrathecal injection	2 patients with MS and painful spasms	None	Observed relief of spasticity	Relief of painful spasms in one case, with improved extension of hips and knees. Relief of painful spasms on right, but not left, in second case	Not applicable

continued

TABLE 19 Phenol (cont'd)

Study	Design	Drugs and dose	Patients	Withdrawals	Outcomes measured	Results	Trial quality (Jadad)
Wassef (1993), USA ⁷⁸	Comparison of two approaches to obturator block	Phenol in glycerine: 5 ml 6% solution administered by traditional or interadductor approach to obturator nerve	10 patients in each group, of whom 3 (in each group) had MS	None	<p>Percentage of block success.</p> <p>Muscle spasm score (<i>ad hoc</i> scale from 1 to 4).</p> <p>Hygiene score (<i>ad hoc</i> scale from 1 to 4).</p> <p>Gait score (<i>ad hoc</i> scale from 1 to 3).</p> <p>Patient satisfaction</p>	<p>Successful block reported in 81.4% of cases following interadductor approach, 60.5% of cases following traditional approach.</p> <p>Reduced from 3.3 to 1.3 following interadductor approach, from 3.2 to 1.7 following traditional approach.</p> <p>Reduced from 3.3 to 1.1 following interadductor approach, from 3.3 to 1.8 following traditional approach.</p> <p>Reduced from 3.0 to 1.3 following interadductor approach, from 3.0 to 1.5 following traditional approach.</p> <p>8/10 completely satisfied or minor reservation in interadductor group, 4/10 in traditional group</p>	Not applicable

Side-effects

Few side-effects are reported in these case series. Complications which are reported include 'further muscle weakness', sensory loss and genitourinary dysfunction following subarachnoid block.⁸⁰ Peripheral nerve blockade other than the obturator nerve (which supplies a very small area of skin, and that is partially supplied by other nerves) is reported to result in anaesthetic skin and sometimes persistent severe pain.⁸¹ Arachnoiditis and sphincter dysfunction following intrathecal injection are also referred to.⁸²

Summary

The only evidence which we were able to identify with regard to the effectiveness of phenol blockade in treating spasticity was of low grade, being essentially only case series. Nevertheless, in the light of the stable or deteriorating nature of spasticity, and the prompt relief observed in a high proportion of cases, it is reasonable to conclude that phenol injections do relieve spasticity, with a duration of action of some months. There is insufficient evidence to draw firm conclusions about the functional impact of this relief of spasticity, although it is likely that in some cases significant advantage may be gained. Peripheral nerve or motor point blockade is likely to lead to fewer complications than intrathecal block.

Threonine

Threonine is an amino acid. It is not licensed as a prescription drug in the UK. Two studies of its use for the treatment of spasticity in patients with MS were identified. Both were DB, crossover RCTs. The study design, outcome measures and results are detailed in *Table 20*. Both were of a high quality, achieving a Jaded score of 5/5.⁸³ No data are available on the cost of threonine, although it is thought to be inexpensive.

In the first study,⁸³ of the various outcome measures used, only one showed a difference, with $p = 0.036$. It is possible that with the multiple testing involved this represents a Type I error. Furthermore, as the paper did not include a power calculation, and in view of its small size, it is possible that the study was underpowered.

As the postulated mechanism of action of threonine is to increase spinal glycine levels, the finding that the CSF glycine concentration was not altered (although plasma and CSF threonine levels were), indicates that threonine, at least at the dosage used, is ineffective.

In the second study,⁸⁴ a sequential analysis was undertaken. Patients were assessed using the Ashworth scale, with the six highest of 10 passive movements summed to give a 'spasticity score' and a 10% reduction in this score taken to be a response to treatment. The study was stopped after 33 patients were recruited because of a statistically significant benefit from threonine. Both spasticity score and spasm score (frequency \times severity) were reduced more on threonine than on placebo, but there was no change in the Barthel index or the Kurtzke disability status scale (DSS). The plasma threonine level was significantly higher in the treatment than placebo arm (498 versus 184 $\mu\text{mol/l}$). There was no significant change in plasma glycine. The correlation between plasma threonine levels and spasticity reduction or spasm score was poor.

Vigabatrin

One review of pharmacodynamic and pharmacokinetic properties of vigabatrin was identified. This indicated that there was some early phase trial work which showed that vigabatrin ameliorated spasms and improved some parameters of spasticity to a small or moderate extent, including reducing the frequency of spasms and the associated pain. Some of this work was carried out on patients with MS, but it is not possible to describe the findings in more detail since these data are on file with Marion Merrell Dow. The cost of vigabatrin is £44.85 for 100 500-mg tablets. The maximum dose is 3 g per day. At this dosage, the cost per day would be £2.69. It is an anticonvulsant, and as such is not licensed specifically for use in the treatment of spasticity.

Clonidine

Two studies of clonidine in the treatment of spasticity were identified from the scoping review. Both were excluded, the first because the study did not include patients with MS and the second because it took the form of a letter with anecdotal evidence on three case histories.

Methylprednisolone

Compton and Swingler suggest that intravenous methylprednisolone is a treatment for spasticity, but do not cite any evidence to support this.⁴ Neither did there appear to be any evidence of current clinical usage to this end. Intravenous methylprednisolone is used to reduce the length of episodes of relapse, and its effect reduces with increased use. No research studies were identified

TABLE 20 Threonine vs placebo

Study	Design	Drugs and dose	Patients	Withdrawals	Method of assessment	Outcomes	Trial quality (Jadad)
Hauser <i>et al.</i> (1992), USA ⁸³	DB crossover RCT	Threonine 2.5 g t.d.s. Placebo. 2 × 8-week treatment periods separated by a 2-week wash-out	N = 26. All had clinically definite MS. Mean age 41 y. 15 F, 11 M. Mean disease duration 12 y. Mean EDSS score 4.7. Ambulatory patients with inactive or slowly progressive MS	N = 5, 2 during the 1st treatment period, 3 during the 2nd treatment period. One case due to additional antispasticity medication being initiated, the others apparently unrelated	EDSS. AMB. Ashworth scale. Clinician spasticity scale. Patient spasticity scale. Clinician global assessment. Patient global assessment. EMG measures. CSF glycine	Not stated. Not stated. No difference. 11 patients improved on threonine vs 5 on placebo ($p = 0.036$). No difference. No difference. No difference. No difference.	5/5 Data analysis is correctly based on only those that completed both arms of the crossover
Lee and Patterson (1993), UK ⁸⁴	DB cross-over sequential analysis RCT	L-Threonine 6 g/day. Placebo. 4-week baseline, 2-week treatment, 2-week washout, 2-week treatment	N = 33. 23 had MS. 11 F, 12 M. Ages 35–66 y. DSS 6–9.	N = 4 in baseline period because of excessive variability in spasticity	Ashworth scale – six highest of 10 passive movements summed to give 'spasticity score'. A 10% reduction in score is defined as response to treatment. Spasm score (frequency × severity). Barthel index. Kurtzke DSS	Study stopped after 33 patients because of significant benefit from L-threonine. 16 responded to L-threonine, 3 to placebo, 8 to neither, 2 to both. Mean (?29 patients) spasticity score reduced from 21.5 to 18.9 on L-threonine, 21.5 to 20.6 on placebo. Reduced from 3.8 to 2.6 on L-threonine, 3.4 to 3.0 on placebo. No change. No change. 1 patient reported indigestion and 1 diarrhoea on threonine	5/5

which include methylprednisolone in the treatment of spasticity.

Cyproheptadine

One report of the use of cyproheptadine, a serotonergic antagonist, in the treatment of spasticity was identified.⁸⁵ Six patients, four of whom had MS, were given cyproheptadine in doses up to 24 mg/day over periods varying from 4 to 24 months. It was an open study, without any controls. Cyproheptadine was reported as significantly decreasing ankle clonus and spontaneous spasms. Walking was said to improve in four of the patients (two with MS).

Magnesium

A single case report of the effect of magnesium glycerophosphate on spasticity in a 35-year-old woman with MS was identified.⁸⁶ At a dose of 1000 mg/day, there was a reduction in the mean Ashworth score for 10 lower limb movements of 0.7 points (from 4.9 to 4.2). Nursing care was said to have been facilitated.

Clinical effectiveness of treatments for spasticity – summary

On the basis of the evidence reviewed above, drug treatments for spasticity may be categorised into three groups. Baclofen, dantrolene, diazepam and tizanidine are all oral treatments. They all differ in the pharmacological mode of action, but all appear to be moderately effective in reducing spasticity (as measured using the Ashworth scale or other clinical measure). The evidence of effectiveness is stronger for tizanidine than for the other three, possibly reflecting its more recent development, at a time of more stringent requirements for establishing effectiveness. Very little evidence is available as to the effect of these drugs on functional ability in patients with spasticity, and what there is does not suggest any effect. There is no evidence that any one drug is more effective than any other, but side-effects appear to be most common with diazepam and dantrolene and least common with tizanidine.

BT (administered intramuscularly), intrathecal baclofen and phenol injections are effective in reducing spasticity (although the evidence base for phenol is less good than for the other two drugs). All three are invasive treatments, have a longer term effect and are more costly than oral treatment. BT has its effect by causing paralysis of the treated muscle, so is only appropriate when the loss of muscle tone is of greater functional benefit than maintaining spasticity and power. Intrathecal baclofen requires the insertion of a

permanent indwelling intrathecal catheter and pump, which gives rise to the risk of infection and other serious side-effects. In practice, these considerations mean that these treatments are only appropriate for patients with severe spasticity, in whom functional ability and QoL are severely impaired.

Other possible drug treatments for spasticity include threonine, vigabatrin, clonidine, methylprednisolone, cyproheptadine and magnesium. The authors were not able to identify any good evidence to establish the effectiveness or otherwise of these treatments.

Economic evidence

The results of the searches described in Chapter 3 were used to identify economic evidence relating to treatments for pain and spasticity in MS.

Despite a broad search strategy on economic studies, no formal cost-effectiveness analyses for any of the included indications were found. Although literature was found on treatment effectiveness, implying potential economic benefits through the improved management of patients, none of these papers attempted to calculate formal cost-effectiveness ratios, estimates of utility or overall treatment costs.

The four studies which most closely approximated to formal health economic evaluations dealt with the use of CIBI in the treatment of MS-related spasticity and its impact on hospitalisation rates. This economic review is, therefore, restricted to those studies. No formal economic review has been undertaken of the other treatments for spasticity, or treatments for pain.

Patients with severe spasticity frequently require hospitalisation for the treatment of related problems. These include the management of bedsores due to long-term immobility and respite care. Hospital stays may last as long as several months. The impact on hospitalisation requirements following CIBI have been reported for the USA,⁸⁷ Canada^{68,88} and The Netherlands.⁸⁹ These four studies are summarised in *Table 21*.

The cause of spasticity in these studies is not always MS. Causes include cerebral damage and spinal cord injury (SCI). Generalisation of the results specifically to MS patients may not, therefore, be valid. The studies were also

TABLE 21 Economic studies of intrathecal baclofen

Study	Patients' characteristics	Method	Results	Savings and comments
Nance <i>et al.</i> (1995) ⁸⁸	6 patients. SCI or MS	Comparison of hospital admissions, causally related to spasticity, 2 years prior to treatment, 2 years post treatment	<p>Prior 2 years: 376 in patient hospital days (range: 0–186, average 63 days). Post 2 years: 136 inpatient days (range: 11–36, average 23 days), none of which was due to spasticity. All admissions post-CIBI were related to screening, implantation, treatment of problems related to the intrathecal drug delivery devices and problems related to marked reduction in muscle tone</p>	<p>The authors report average net savings of Can\$25,250 per patient, taking account of the cost of pump and hospital days (average cost per inpatient day Can\$813). The authors consider the treatment to be cost-effective.</p> <p>Using UK costs of £211 per inpatient day, there would be savings of £8440 over 2 years in reductions of hospital days. This would balance the cost of the pump.</p> <p>The number of days used within the post-CIBI years may be overestimated owing to use of placebo days in the screening phase.</p> <p>2 patients reported ability to decrease personal attendant services and 1 patient obtained employment following CIBI. 2 patients had skin ulcers which healed following CIBI</p>
Postma <i>et al.</i> (1999) ⁸⁹	18 patients undergoing CIBI (11 MS, 7 SCI). 15 matched patients of similar age, sex and diagnosis (9 MS, 6 SCI)	Comparison of the number of days in hospital between groups 1 year prior to implantation and 1 year following implantation	<p>Average number of hospital days in year of implant in treated group was 31.5; 9.9 in the test phase, 12.3 for the implantation phase and 8.4 resulting from complications. Average number of hospital days 18.7 for the matched patients. In the year following implantation no significant difference was found</p>	<p>A calculation of the average direct costs that would be likely to occur in a non-experimental situation was made in this study. For this analysis only 2 days were allocated to the test phase, 10.3 days for the implantation phase and, again, 8.4 days for complications. If this had been the case, the average number of days for the treated group would have been 20.7, i.e. only 2 additional days in comparison to the matched group.</p> <p>For the non-experimental situation, the total average cost of selection, testing, implantation and medical follow-up amounted to US\$28,473 per patient for the first year. Full breakdown given in the paper.</p>

continued

TABLE 21 Economic studies of intrathecal baclofen (cont'd)

Study	Patients' characteristics	Method	Results	Savings and comments
Becker <i>et al.</i> (1995) ⁶⁸	9 patients. 6 MS, 2 cervical SCI and 1 head injury	Hospitalisation costs 1 year prior and one year post-implantation	Prior to implantation: 755 acute hospital days (range: 0–319, average 84 days). Year of implantation: 259 days (range: 10–48, average 29 days)	Based on cost of hospital stay of Can\$570 per day, reductions in hospital days give average saving of Can\$31,000 per patient (excluding pump and implant). Using UK costs of £2111 per inpatient day, there would be savings of £11,660 within the first year in reductions of hospital days. This would balance the cost of the pump. At time of implantation, 6 of the 9 patients were institutionalised in either chronic or acute care hospitals owing to problems managing their spasticity. Following CIBI, 3 patients were discharged after prolonged hospitalisation, 2 to their own home and 1 to a group home. Savings are likely to be underestimated as 2 patients were in chronic care institutions prior to implantation and, thus, would not have required acute care. Authors conclude CIBI to be beneficial in terms of nursing assessment, patient satisfaction and cost-effectiveness
Ordia <i>et al.</i> (1996) ⁸⁷	10 patients. Spasticity of spinal cord origin, MS or SCI. 59 patients in total had pump implant, but only the first 10 were included in the cost study	Number of bed days used for 1 year prior and 1 year following implantation. Hospitalisations were all cause and not specifically related to spasticity	Prior to implantation: 95 bed days. Post-implantation: 68 bed days, i.e. 2.7 days per patient saved for general hospitalisations in 1 year. Also 58 days used for screening and implantation, i.e. 5.8 days used per patient for the screening and implantation	This study does not report the proportion of days that are related to spasticity, and, thus, may include admissions for unrelated causes. Similarly, there is no information as to the number of post-implant bed days that are due to complications from the procedure. The number of bed days reported is low as patients who received acute rehabilitation less than 1 year prior to surgery were excluded from cost study. Authors concluded CIBI to be a cost-effective method for treatment of severe intractable spinal spasticity. However, this was based upon an average cost of US\$2500 per day.

conducted in relatively small numbers of patients which again may undermine validity.

The savings reported by Nance and colleagues⁸⁸ and Becker and colleagues⁶⁸ refer only to hospitalisation days related to spasticity. The former reported an average reduction of 40 days in the number of bed days used over 2 years, whereas the latter reported a reduction of 55 bed days used over 1 year. The difference in numbers could be due to a greater degree of disability in the population reported by Becker and colleagues, as there were patients suffering skin breakdown who had considerable resource requirements.

The savings reported by Ordia and colleagues⁸⁷ do not relate specifically to spasticity and no reasons are given for hospitalisation prior to or post-CIBI. These results cannot be used in this analysis without further information.

Postma and colleagues⁸⁹ provide a detailed analysis of the costs and savings of CIBI in The Netherlands. The study showed no significant difference between patients and controls in the number of hospital days in the year following CIBI. For the implantation year there were 18.7 days used on average by the control group compared with an estimated average of 20.7 days related to the CIBI procedure and no further days related to spasticity for the CIBI group.

These papers provide three separate estimates of bed days used for patients without or prior to CIBI: 19 days,⁸⁹ 32 days (63 days over 2 years)⁸⁸ and 84 days.⁶⁸ The differences are almost certainly due to differences in patient selection and care settings. Assuming an average UK cost per inpatient day of £211,⁹⁰ this represents costs of £4000, £6800 and £17,700, respectively.

The number of bed days used during the year of implantation ranges from 21 days⁸⁹ to 29 days.⁶⁸ This corresponds to costs of £4400–6100 for the hospitalisation related to the CIBI procedure.

Overall, these studies imply the likelihood of significant cost off-sets and patient benefits from avoided hospitalisations post-treatment, but they do not attempt to go further in combining this with any form of cost of treatment and overall utility gain per patient.

Estimates of cost utility for CIBI

A recently completed health technology assessment has attempted to estimate a cost per life year gained from the use of CIBI.⁹¹

The cost of CIBI was estimated at around £11,700 for the initial assessment, test procedure, implantation procedure and equipment. This includes a cost of £6770 for the pump. In addition, costs of £870 per annum were indicated for the general maintenance, drug refill and follow-up of patients. An assumption was made that treatment would last for up to 7 years, depending on the type of pump used, although it was noted that life expectancy may be less than this in these MS patients. This equated to a total cost of around £15,900 for a 5-year period and £17,600 for a 7-year period. Discounting costs at a rate of 6% gave a total current value of £15,400 for a 5-year period and £16,700 for a 7-year period.

In the absence of studies reporting upon QoL utilities for CIBI, the report used a generic QoL, the Index of Health Related Quality of Life measure (IHQL), to construct a range of utility estimates.

It was initially assumed that a patient pre-CIBI would be confined to bed (state D7), have severe pain (state P3) and be moderately distressed (anxious and depressed most of the time, but happy and relaxed some of the time) (state E3). Given these scores across the three domains, the average patient was associated with a utility of 0.449.

The post-CIBI patient was assumed to have the same distress and disability, but a reduction in pain to slight pain. This resulted in a revised utility score of 0.675 equating to a utility gain of 0.226. When the initial pain level was judged as only moderate, the QALY utility gain reduced further to 0.149. An improvement in pain to moderate pain levels, with the patient also experiencing a reduction in disability to state D6 (confined to a chair, only able to get out with assistance, very limited ability to perform role functions), resulted in a utility gain of 0.199.

The authors clearly recognised that using a generic scale in this way was not sufficient to provide conclusive economic evidence of cost-effectiveness. However, they did suggest that assuming 5 years' worth of health benefit are obtained from the pump implantation, then an average annual QoL utility gain of around 0.16 would result in a cost-utility ratio of £20,000. The authors argue that this level of shift in utility scores was possible, from the indicative health benefits as calculated in their own estimated QoL analysis, described above.

Summary of economic evaluation

Although effectively no published information related to the economic impact of treatments for pain and spasticity was found, it is useful to recap on the likely areas of cost impact of treatment. These are the areas in which cost offsets could be achieved, in addition to health benefits provided to the patient.

Pressure sores/ulcers

Pressure sores are a considerable risk for patients who are bed-bound owing to spasticity. The cost of treating pressure sores is substantial, as they require either long periods of hospitalisation or intensive community nursing care. For example, a full thickened sacral ulcer extends hospital stay by over 25 weeks at a cost of £26,000 including extra staffing, drugs, dressings and hospital overheads.⁹² Costs for pressure ulcers differ depending on the ulcer stage, and also vary depending on care setting. Local estimates of costs for treating pressure sores are around £17,000 for a grade 4 pressure sore and £5000 for grade 3/4 (McClelland MR, personal communication, 1999). Research is lacking in many areas of pressure ulcer prevention and treatments with regards to cost-effectiveness. It is estimated that the total national cost in the UK for the treatment of pressure sores is approximately £755 million per year.⁹²

Orthopaedic surgery

Treatments may defer the onset of muscle contractures and hip dislocations and potentially delay or inhibit the onset of scoliosis. Although it is not clear whether these procedures have been avoided or merely delayed, there is clearly potential for cost savings.

Reductions in oral treatments or other interventions

The cost of CIBI should be offset by reductions in oral treatments. The use of CIBI may also reduce the need for interventions such as therapeutic nerve blocks.

Aids and adaptations

Improved management of spasticity may lead to a reduction in the need for seating aids, wheelchairs, spinal jackets and orthoses. Reductions in spasticity have also been reported to decrease the need for specially designed wheelchairs designed to accommodate extended legs, and thus allow patients to switch to less expensive compact models. The compact wheelchair means that there is no need for remodelling of the home, and fewer adaptations are required.

There are currently no data available to quantify these potential savings, although anecdotal evidence suggests that the savings will be realised. Examples of potential cost savings from the reduced need for home adaptations are as follows:

- redesign bathroom: £1925 (median)
- redesign kitchen: £2282 (median).⁹⁰

Reductions in care resources

One area of potentially significant savings is the reduction in carers' time and the need for nursing home care following a reduction in spasticity. Owing to the intensity of care required for patients with severe spasticity, any reductions in care requirements will lead to considerable cost savings.

Improved sleep may lead to reductions in night care and patients will be able to be seated and dressed more easily, sometimes reducing the number of carers required. Although reductions in the caregiving time required and greater ease of care are frequently reported in effectiveness studies, there is no quantification of the savings which may be realised.

Discussion and conclusions

The literature reviewed suggests that there is limited evidence of the effectiveness of four oral drugs for spasticity – baclofen, dantrolene, diazepam and tizanidine – when used orally for the treatment of spasticity. All appear to be approximately equally effective when assessed clinically, though in no case is there any good evidence of functional benefit.

Baclofen

- For oral baclofen, 16 studies were identified and 12 included. All were DB controlled trials and 11 of the 12 were randomised. They achieved Jadad scores of between 2 and 4.
- Patients preferred baclofen over diazepam owing to fewer side-effects.
- None of the comparisons with placebo was able to show any improvement in functional ability.
- The Cochrane review of pharmacological interventions for spasticity following spinal cord injury published in 2002 noted that there is some evidence that oral baclofen is effective against placebo, but the outcome measures used are of limited clinical relevance.⁹³

Dantrolene

- Ten papers were identified and six included. Five were DB RCTs and the fifth was an open

study. Five studies were against placebo and one against diazepam. The Jadad scores were low, ranging from 0 to 4.

- Dantrolene appeared to have a moderate effect in reducing spasticity, but this was undermined by the number of patients experiencing side-effects, weakness in particular.

Diazepam

- Seven studies including diazepam were identified. Only one of these was placebo controlled. The other six were comparative studies against active drugs where diazepam was the comparator.
- Diazepam is effective in reducing the Ashworth score but was no more effective in comparison with other drugs.
- Diazepam has considerable side-effects which patients do not like, predominantly sedation and weakness.

Tizanidine

- Sixteen studies were identified and 12 were included. These were all DB controlled trials. Five of these were comparisons against placebo.
- Tizanidine appears more effective against placebo in the two single-dose trials, but there is little evidence of increased effectiveness over and above placebo in the trials of longer treatment. Only one out of three studies comparing tizanidine with placebo showed a statically significant difference in the Ashworth score and in this study there was no difference from placebo in terms of muscle spasms.
- Tizanidine appears only equally effective as baclofen or dantrolene. Tizanidine shows effectiveness in improving muscle tone and frequency of spasms, but this is not translated into improvements in functional ability.
- In terms of tolerability, only two of the studies showed tizanidine caused less muscle weakness than other drugs.
- The Cochrane review of pharmacological interventions for spasticity following SCI noted that tizanidine produced a large number of adverse events, notably drowsiness and dry mouth, in some cases causing withdrawal from the studies.⁹⁴
- Tizanidine is far more expensive than other oral therapies. At the recommended dosage the average daily cost of tizanidine is £4.49 per day compared with a daily cost of £2.58 for oral baclofen at its maximum daily dosage.

There is no good evidence of effectiveness for gabapentin, threonine, vigabatrin, methylprednisolone, cyprohepladine and

magnesium. The Cochrane review of antispasticity agents for MS published in 2002 included just 13 studies and found that the test drugs only produced statistically significant results in three out of six placebo controlled trials.⁸ They included seven comparative studies with other drugs and found that there were no statistically significant differences between the drugs in any of the seven studies. They concluded that as a result of lack of evidence, no prescribing recommendations could be made.

This report has been less restrictive than the Cochrane review in terms of the studies included in the analysis. Some of the studies included here have very low Jadad scores and even though some studies had higher Jadad scores, there are still limitations to some of these studies. The Jadad scoring system has been criticised as being an appraisal of the quality of reporting rather than the quality of the trial itself. For instance, the Jadad score takes account of whether or not withdrawals are reported but not how many withdrawals there were, or their reasons for withdrawing. The Jadad score also takes no account of the sample size and whether the study has adequate power.

In terms of the more invasive drug treatments for spasticity, there appears to be limited evidence for the effectiveness of BT and much more evidence (but not all of good quality) that intrathecal baclofen is effective in the treatment of patients with severe spasticity. The evidence that phenol injections are effective is anecdotal.

BT

- 12 studies were identified and five were included. Three were DB placebo-controlled trials and two were open studies. The two open studies had Jadad scores of 0 whereas the three RCTs had Jadad scores of 5.
- The evidence for effectiveness was very limited. Most studies showed an improvement in the Ashworth score, but this does not always translate into functional improvement. Only one RCT showed a statistically significant improvement in the hygiene score.
- A Cochrane review of BT A in the treatment of lower limb spasticity in cerebral palsy published in 2002 found only three eligible studies and concluded that there is no strong evidence to support the role of BT in treating spasticity.⁹⁴
- BT eliminates spasticity through causing paralysis. This can cause unwanted muscle weakening and means that BT is best suited for

patients with the most severe spasticity and where muscle strength is no longer required.

Intrathecal baclofen

- 20 studies were identified and 15 included in this review. Only two of these studies took the form of DB RCTs, the remainder being open-label studies. Only one study obtained a Jadad score of 5. The sample sizes also tended to be small.
- There is evidence that intrathecal baclofen is effective in reducing spasticity in terms of both muscle tone and frequency of spasms. The studies indicate that patients have an improved ability to sit in a wheelchair and ability to stand and easier transfers. Improvements were also noted in SIP and ADL scores.
- Intrathecal baclofen requires the installation of a pump, depot and intrathecal catheter. Their use is, thus, most appropriately restricted to people with severe disabling spasticity.
- With regard to more severe spasticity, the numbers quoted as receiving a pump implant for intrathecal baclofen seem very low compared with the potential number of patients with spasticity severe enough to benefit from this technique.
- Although intrathecal baclofen exposes the patient to certain risks and complications, there is clear evidence that it is an effective treatment. Carers and nursing staff are also in a position to benefit from the use of intrathecal baclofen as the patient becomes easier to nurse and hygiene can be maintained.
- Economic evaluation of intrathecal baclofen suggests that although expensive, its use may be associated with significant savings in hospitalisation costs. Further research is required to establish reliably its cost-effectiveness.
- Other reviews of pharmacological interventions for spasticity from other causes have also identified intrathecal baclofen as an effective treatment. Creedon and colleagues carried out a meta-analysis of intrathecal baclofen for severe spasticity including studies published prior to June 1996.⁹ They found statistically significant changes in both the Ashworth score and the spasm score before and after treatment in all patients, but particularly in patients with MS, and spinal cord injuries. The results for those with cerebral palsy were not statistically significant but did show a trend towards improvement. This may have been due to the low numbers of patients with cerebral palsy included in the meta-analysis. It should also be noted that the Creedon study showed that 92%

of those who had a pump installed were still using the pump at 1 year of follow-up, which indicates that problems experienced with the pump and catheter may be minor.

- The Trent Institute for Health Services Research carried out a review of the effectiveness of intrathecal baclofen in the management of patients with severe spasticity and building on the Creedon review went on to look at functional outcome measures. They found that intrathecal baclofen led to functional improvements including improvements in the ability to sit up in bed or to sit more comfortably in a wheelchair; improved nursing care and moderate improvements in ADL.⁹¹
- The Cochrane review of pharmacological interventions for spasticity following SCI, last updated in 2000, covered nine studies, of which three involved intrathecal baclofen. The reviewers concluded that two of the studies showed that intrathecal baclofen had a significant effect in reducing spasticity compared with placebo. However, they noted that use of intrathecal baclofen is an expensive, demanding process and that its use should be restricted only to true non-responders, identified through a careful assessment of the extent of non-response.⁹³

Non-drug therapies for spasticity

There are a number of possible non-drug therapies which are employed to assist with spasticity in MS:

- Neurotomy – there is anecdotal evidence that selective neurotomy can be helpful in reducing spasticity, but it is really only suitable when the spasticity affects just a single joint.
- Myelotomy – myelotomy has anecdotally a good success rate according to Shetter,⁹⁵ but it is not reversible. There appears to be little or no evidence in patients with MS.
- Chronic cerebellar stimulation (CCS) – a review of CCS, which is used to reduce spasticity caused by cerebral palsy, found that CCS resulted in an 85% reduction in spasticity. How the change in spasticity was measured is not clear.⁹⁶
- Microsurgical DREZ-otomy (surgical sectioning of nerves in the dorsal root entry zone) – there is some evidence of DREZ for the treatment of spasticity and pain in MS.⁹⁷

Conclusions

Overall, there is limited evidence for the effectiveness of oral therapies for moderate spasticity. Diazepam is particularly disliked by

patients because of its side-effects. There is little evidence that tizanidine, despite its extra cost, is any more effective than other oral therapies such as baclofen and dantrolene. The findings of this review are supported by reviews of the same treatments for spasticity derived from other aetiologies. It is debatable whether or not the effectiveness of treatments for spasticity of aetiologies other than MS, such as SCI or stroke, can be compared. Nevertheless, the evidence from other reviews suggests that the effectiveness of oral antispasticity agents is very weak, despite their widespread usage.

The evidence for intrathecal drug treatment for severe spasticity is stronger, particularly in relation to intrathecal baclofen. It is believed that the appropriate use of intrathecal baclofen could result in significant savings in hospitalisation costs in relation to bed-bound patients who are at risk of developing pressure sores.

There is a great need for more research into the clinical and cost-effectiveness of treatments for spasticity, in MS including the development of better outcome measures which relate to functional ability and patients' QoL.

Chapter 5

Pain in MS

Scope of review

This review addresses the questions of what the treatments currently available for the management of pain in MS are and what the effectiveness (*and cost-effectiveness*) of those treatments is. It concentrates in particular on medical (pharmacological) treatments, and does not explicitly look at the effectiveness of surgery, psychological or complementary therapies. Although there is a strong belief among many patients with MS that cannabis provides effective relief for pain (and spasticity) in the condition, it is not included in this review. If clinical trials of good quality are completed looking at the effectiveness of cannabis, or its derivatives or constituents, we may be in the ironic position of having better evidence of its effectiveness than any of the currently used drugs.

Prevalence

For some decades, the received wisdom appears to have been that MS did not cause, or only rarely caused, pain. This is now recognised to be far from the case. Observational studies of patients attending neurology clinics have reported prevalence of pain between 28.8 and 86% (see *Table 22*). Differences in prevalence may be due to a variety of factors, including the selection of patients, definition of pain syndromes, means by which the information is collected (notes review versus questionnaire) and inclusion or exclusion of pain thought not to be directly caused by MS. The results of studies are summarised in *Table 22*.

It is clear, therefore, that pain is a common problem for patients with the disease. Because of its often chronic nature, and the particularly unpleasant character it can sometimes have, it may be a very major cause of impaired QoL. Further, because it is essentially subjective, and because the treatment offered may be very variable (see below), some patients may feel that they are not being taken seriously by clinicians, which in itself exacerbates the problems.

The authors were not able to identify any studies which looked explicitly at the impact of pain on

the QoL of patients with MS, or any which sought to correlate pain symptoms with prognosis. A number of surveys of patients with MS which sought to identify the prevalence of pain as a symptom also examined whether there was any association between pain and disability.

Brochet and colleagues⁹⁸ reported a correlation between pain and higher levels of disability, as measured by the DSS. Archibald and colleagues⁹⁹ found no difference between the pain and no-pain groups in the Kurtze EDSS, but did find that those with pain had a significantly lower score on the Mental Health Inventory (MHI) (mean 159.2, SD. 28.4, versus mean 170.4, SD. 25.8, $p < 0.05$). Indaco and colleagues¹⁰⁰ did not identify any difference between patients reporting pain and those who did not in terms of the DSS, Hamilton Rating Depression Scale or Beck Self Depression Inventory.

Three studies give some information as to the overall impact of pain on daily life. Warnell¹⁰¹ reported that 49% of patients stated that pain compromised their ability to work (although pain-free patients were not more likely to be employed than those reporting pain); 44% said pain interfered with sleep patterns, and 34% said that it interfered with relationships with family and friends. Rae-Grant and colleagues¹⁰² reported that 5% of respondents identified pain as the worst symptom of their disease. The MS Society survey³ asked responders to identify the three symptoms which caused them the most difficulty or distress; 18% of responders identified pain as one of the three 'worst' symptoms.

Types of pain syndromes (and difficulties in defining and dissociating them)

The manifestations of pain in MS are protean. Pain may either be due directly to nerve damage as part of the underlying pathological process, or it may be secondary to paralysis and immobilisation. Pain syndromes are often categorised as acute or chronic.

Acute pain syndromes (other than optic neuritis) are probably due to ectopic excitation at the sites

TABLE 22 *Observational studies of the prevalence of pain in MS patients*

Lead author	Year	No. of patients (included/eligible)	Patient selection	Information collection	Overall prevalence (%)	Notes
Clifford ¹⁰³	1984	317/317	All patients who had attended outpatient clinic	Notes review	29	Increased prevalence with age and duration of disease
Vermote ¹⁰⁴	1986	83/83	Patients with MS hospitalised for rehabilitation	McGill pain questionnaire	54	Musculoskeletal pain increased in frequency with increasing disability, neurogenic pain did not
Kassirer ¹⁰⁵	1987	28/?	Long-standing MS patients (duration 29 y) at outpatient clinic	Specific questionnaire	75	Patients with long-standing disease, 84% wheelchair bound
Moulin ^{106,107}	1989	159/?	Excluded patients in nursing homes	Specific questionnaire	55	Increased prevalence with age: up to 73% in 60+ y age group
Rolak ¹⁰⁸	1990	104/104	Consecutive patients at private and public clinic	Interviewer took detailed headache history	52 (headache only)	Survey of headache only: optic neuritis and trigeminal neuralgia excluded. Prevalence in control groups 14 and 18%
Warnell ¹⁰¹	1991	258/364	All patients attending outpatient clinic	Specific questionnaire	64	Increased prevalence in the older age groups (81% in 60+ y). No difference in prevalence in different types of MS. 49% of patients stated that pain compromised their ability to work, 44% said pain interfered with sleep patterns and 34% said that it interfered with relationships with family and friends
Stenager ¹⁰⁹	1991	117/124	Random sample of hospitalised patients aged 25–55 y	Specific questionnaire, structured interview, neurological examination	65	Increased pain frequency with age and duration of disease
Stenager ¹¹⁰	1995	49/63	Follow-up after 5 y of younger patients in study above	Examination by the same physician as previously	86	Increased frequency of both chronic and acute pain syndromes. Frequency of pain in this subgroup of individuals in the previous study had been 53%
Brochet ⁹⁸	1992	108/?	All patients attending outpatient clinic	Specific questionnaire	41	Patients with pain slightly older, had disease of longer duration and more likely to have progressive MS. Correlation between pain and higher levels of disability, as measured by the DSS
Archibald ⁹⁹	1994	85/94	Patients referred to outpatient clinic	Structured interview, MHI	53	Pain prevalence not correlated with age or disease type. No difference between the pain and no-pain groups in the EDSS. MHI score lower for patients with pain than those without

continued

TABLE 22 *Observational studies of the prevalence of pain in MS patients (cont'd)*

Lead author	Year	No. of patients (included/eligible)	Patient selection	Information collection	Overall prevalence (%)	Notes
Indaco ¹⁰⁰	1994	122/?	Patients admitted to the clinic with MS. Patients with headache and those whose pain was relieved by analgesics excluded	Structured interview	57	21% of patients had pain at the onset of their disease. Most common pain syndromes were chronic. No difference between patients reporting pain and those who did not in terms of the DSS, Hamilton Rating Depression Scale or Beck Self Depression Inventory
MS Society ³	1997	223/275	MS Society members who had attended recent meetings	Specific questionnaire	54	54% of responders were currently suffering from pain. 18% of responders rated it as one of the worst 3 symptoms. Of the 74% of responders who had spasticity, 77% reported that it was associated with some pain
Rae-Grant ¹⁰²	1999	224/387	Patients identified through practices of local neurologists who were able to complete questionnaire, plus 100 controls	Specific questionnaire	67	Overall 67% reported having had pain (same as controls), but 44% reported active pain (22% of controls). No increase with duration of disease. 5% said pain was the worst symptom of the disease

of demyelination. Sometimes, as with Lhermitte's sign, it is a purely subjective matter as to whether or not the symptom can be described as painful. Acute pain syndromes include:

- Trigeminal neuralgia; clinically indistinguishable from idiopathic trigeminal neuralgia. May be the first manifestation of MS. Bilateral trigeminal neuralgia is said by some to be pathognomonic of MS. Glossopharyngeal neuralgia is less common, but also seen.
- Lhermitte's sign; an electrical sensation passing down the back to the legs on flexion of the neck.
- Acute radicular pain; may be the presenting symptom of MS.
- Tic-like extremity pain.
- Dysaesthetic limb pain.
- Painful tonic seizures; painful tonic seizures may be associated with paroxysms of tic-like or dysaesthetic pain.
- Optic neuritis; aching retro-orbital pain exacerbated by eye movement, probably caused by inflammation of the meninges surrounding the optic nerve.
- Painful bladder spasms.
- Headache; there are conflicting reports as to whether headache is more common in patients with MS and, if so, what the association is.^{111,112}

Chronic pain syndromes may be due to neuronal damage to the spinothalamic pain pathways. In general, they appear to be more common in older people and people who have longer duration of disease (see above). Chronic pain syndromes include:

- Dysaesthetic extremity pain; commonest pain syndrome in MS. Continuous burning, aching or throbbing pain, particularly in the legs and feet, is common. Although the pathophysiology is unclear, it is frequently associated with spinothalamic sensory loss.
- Painful spasticity; spasticity is common in advanced MS, and is often painful. Often precipitated by tactile stimulation.
- Visceral pain.

Many patients develop secondary pain as a result of MS-related disability. The most common manifestation is back pain, particularly in patients confined to wheelchairs. Spastic weakness produces abnormal stress on the paravertebral musculature, and can accelerate degenerative disc and facet joint disease. Abnormal gait may also contribute to spinal stress. Spinal disease may also be exacerbated by vertebral compression fractures

as a result of steroid-induced osteoporosis. Immobilisation may also lead to pressure sores. Secondary visceral pain may also arise as a result of constipation.

Individual patients may suffer more than one type of MS-related pain during the course of their illnesses.

Current clinical practice

We were not able to identify any formal review of current clinical practice regarding the treatment of pain in MS. There is evidence, however, that despite the high prevalence of pain as a symptom in MS, very few patients are referred to pain specialists – fewer than 2% in the MS Society survey.³

Access to specialist pain services appears to be very variable, and to depend to a large extent on the interests and availability of neurologists, specialist nurses and anaesthetists. The extent to which patients with MS have access to neurologists appears to be variable. The extent to which neurologists have an interest in pain relief, or have access to pain clinics, specialist nurses, anaesthetists and supporting services (physiotherapy, wheelchairs, etc.) appears variable. The approaches taken by different pain specialists also varies. Overall, therefore, the experience of individual patients with pain related to MS will be very variable indeed.

Clinicians (neurologists and specialist nurses) who have an interest in the treatment of pain in MS emphasise that identifying the nature of the pain is important – in particular distinguishing between pain which is caused by the MS pathology itself, and that which is secondary to MS-related disability. In most cases, pain is a long-standing symptom, which will, therefore, require chronic treatment. The psychological management of the problem is also seen as important, whether simply in terms of the one to one relationship between clinician and patient, or more formally in terms of pain management programmes.

Where pain is secondary to MS-related disability, such as inappropriate choice or use of wheelchairs, or abnormal gait, adequate support from the appropriate service is important. In these circumstances, many patients do not wish to take more medication, and transcutaneous electrical nerve stimulation (TENS) treatment, or trigger-point injections with local anaesthetic or steroid, may be more acceptable.

Certain treatments for pain in MS appear to be commonly used and may, therefore, be called standard. Trigeminal neuralgia is routinely treated with carbamazepine, with phenytoin often used as a second choice (or adjunct) if it is not effective. Gabapentin is also increasingly used as first-line treatment, most particularly since its licensing for neuropathic pain.

Dysaesthetic limb pains are often treated initially with tricyclic antidepressants, with anticonvulsants (carbamazepine or phenytoin) often used as second-line treatment. Beyond this, we do not have adequate information from which to generalise.

There is anecdotal evidence based on clinical experience for a wide variety of non-pharmacological approaches to pain control being used and found to be of value. These include aromatherapy, acupuncture, reflexology, relaxation, electroacupuncture and TENS. In some

cases these treatments can be self-applied or applied by patients' partners. Surgical treatment, such as microvascular decompression for trigeminal neuralgia, is another therapeutic option, although uptake is very variable.

One service model, which appears to be of considerable value even if unusual, is to have a specialist pain nurse working within an MS clinic. In this way, expertise with regard to the management of pain is made available not only to the patients, but also to the MS clinic staff. It is, therefore, likely to lead to an increase in the availability of effective pain relief.

It is noteworthy that most of the drugs used to treat pain in MS are being used out of licence. Carbamazepine is licensed for use in trigeminal neuralgia (aetiology unspecified) and phenytoin as second-line treatment for the same condition. Otherwise, none of the drugs discussed below is licensed for pain relief in MS in the UK.

Chapter 6

Review of the treatment of pain in MS: methods

Formal scoping review

The aim of the search was to identify treatments for inclusion in the review, and to locate relevant RCTs, reviews and cost-effectiveness studies. The search methods were based on the methods used for the review of treatments for spasticity described in Chapter 3.

Initial scoping searches were conducted to identify references relating to MS and pain. The main aims of the initial searches were twofold: to identify interventions to contribute to the framework of treatments considered in the review; and to identify search terms to inform the development of further, comprehensive search strategies. Therefore, search strategies, at this stage, were designed to optimise the specificity of the search results. The searches were undertaken in July 2000 on MEDLINE, EMBASE and the Science Citation Index. Search results were not limited by date, language or by study or publication type.

Comprehensive search strategies were then constructed to identify papers relating to MS and the individual treatments for pain and to MS and individual pain types. Search results were not restricted by date, but were restricted to English language only. Filters to limit search results to RCTs, reviews or cost-effectiveness studies were applied. Searches were undertaken in July and August 2000 on the following databases:

- MEDLINE
- EMBASE

- Science Citation Index
- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL/CCTR (Cochrane Controlled Trials Register)
- PubMed
- HealthSTAR
- Best Evidence
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- AMED (Allied and Complementary Medicine)
- NHS CRD DARE (Database of Abstracts of Reviews of Effectiveness)
- NHS CRD NHS EED (NHS Economic Evaluation Database)
- NHS CRD HTA (Health Technology Assessment).

Search strategies for MEDLINE are given in Appendix 3. Search strategies for other databases are available from the authors.

In addition to searches of electronic bibliographic databases, sources were consulted to identify studies not retrieved through database searching, current research and grey literature. The National Research Register (NRR), MRC Clinical Trials Register and the US NIH Clinical Trials Register were searched. The publication lists and current research registers of health technology assessment and guideline-producing agencies and funding and regulatory bodies were consulted.

Searches were repeated in March 2002.

Chapter 7

Review of the treatment of pain in MS: results

Scope and quality of research evidence

There is a glaring dissociation between the published evidence regarding the effectiveness of treatments for pain and what appears to be current clinical practice. This does not, of course, mean that treatments currently being used are not evidence-based, still less that they are ineffective. What it does mean is that the evidence on which they are based is largely clinical experience, the teaching of others and anecdote. It also militates against effective treatments being consistently used throughout the NHS.

Although the authors were able to identify a large number of papers which related to pain in MS and its treatment, most of these were review articles, or small case series or individual case reports. It was not possible to identify any RCTs whose prime purpose was to examine the treatment of pain specifically in patients with MS. We identified two which looked at the effect of a drug on spasticity in patients with MS, and reported on the effect on pain,^{50,51} and one further one which looked specifically at the effect of intrathecal baclofen on pain,¹¹³ but not exclusively in MS patients.

Drugs considered

The drug most frequently mentioned in review articles was carbamazepine, in particular in the context of the treatment of trigeminal neuralgia. Other drugs which were mentioned in numerous articles were steroids (particularly for optic neuritis), baclofen (oral and intrathecal), gabapentin and phenytoin. A number of drugs are mentioned only in single papers describing case series (misoprostol, octreotide, acetazolamide). Remarkably, there do not appear to be any studies which specifically examined the efficacy of tricyclic antidepressants, which may be considered 'standard' treatment for dysaesthetic limb pain (see above).

Outcome measures

There is no consistency regarding the outcome measures used to gauge effectiveness. In many

cases, case reports or short series recorded only that pain had or had not been relieved. Only one study, an open uncontrolled study of gabapentin,¹¹⁴ appears to have used a validated instrument to assess pain, and hence effectiveness. (It should be noted, however, that this instrument was designed for, and validated in, cancer patients.) No study of the effectiveness of treatment used the McGill pain questionnaire, thought by some to be the definitive instrument for pain measurement. Where attempts were made to quantify the effect of treatment, it was usually done by using pain scales from 0 to 3 or from 1 to 10. It was very rare for reports to give any detail of the effect of treatment on patient functioning. However, concern about outcome measures may be academic in view of the paucity of evidence available for review.

The published research evidence is, therefore, clearly very restricted both in scope and in quality. There is a great need for sound research in this area.

Given the almost complete absence of formal research, of any quality, in this area, what follows is a brief summary of information from reviews and case series and reports. Details are also summarised in *Table 23*.

Specific drug treatments

Carbamazepine

Carbamazepine is an anticonvulsant used for the treatment of generalised tonic-clonic and partial seizures. It is also specifically licensed for use in the treatment of trigeminal neuralgia.

Although a mainstay for treatment of trigeminal neuralgia,^{115,116} and also used for the treatment of glossopharyngeal neuralgia¹¹⁷ and other paroxysmal pain,¹¹⁸ no RCTs have been identified which specifically examined the effect of this drug in patients with MS. Trials of its use in idiopathic trigeminal neuralgia have demonstrated clear superiority over placebo, and effectiveness in relieving pain in 70–84% of cases. Indeed, response to carbamazepine is seen by some as a diagnostic test for the condition. A similar degree of efficacy

TABLE 23 Drug treatments for pain syndromes in MS

Treatment	General	Trigeminal (and glossopharyngeal) neuralgia (TGN)	Lhermitte's sign	Paroxysmal limb pain	Optic neuritis	Dysaesthetic limb pain	Thalamic pain	Painful spasms
Carbamazepine	Licensed for use in the treatment of TGN. Dose 400–600 mg daily, occasionally up to 1200 mg	Demonstrated to be effective in the treatment of idiopathic TGN, ^{116,149} and observed to be as effective in MS-related TGN ¹¹⁹	Reported as being effective ¹²³	Reported as being effective in controlling 'painful tonic seizures' ^{120–122}				Reported as being effective in controlling 'painful tonic seizures' ¹²⁰
Phenytoin	Licensed for use as second-line treatment for TGN. Common dose 300 mg daily	Reviews ^{115,116} suggest it is not as effective as carbamazepine at treating TGN, but can be useful as second-line treatment		Reported as being effective in controlling 'painful tonic seizures' ¹²⁰				Reported as being effective in controlling 'painful tonic seizures' ¹²⁰
Gabapentin		Open-label study included 6 patients with TGN in all of whom it was effective. ⁴⁸ Case series of 7 patients reports relief in 6. ¹²⁷ Addition to lamotrigine or carbamazepine reported as bringing relief and allowing reduction of previous drug dose and amelioration of adverse effects ¹²⁸				Open-label study suggests effectiveness in wide variety of pain syndromes, especially 'dysaesthetic pain'. ¹¹⁴ Further report states that it is effective in relieving refractory pain ¹²⁹		Open-label study included 11 patients with painful spasms in 10 of whom it was effective. ⁴⁸ 2 RCTs have shown it to be effective in reducing spasms and associated pain ^{50,51}

continued

TABLE 23 Drug treatments for pain syndromes in MS (cont'd)

Treatment	General	Trigeminal (and glossopharyngeal) neuralgia (TGN)	Lhermitte's sign	Paroxysmal limb pain	Optic neuritis	Dysaesthetic limb pain	Thalamic pain	Painful spasms
Lamotrigine	100	Two cases report that relief was obtained in 5/5 and 16/18 patients ^{132,133}		Case series reported benefit in patients with paroxysmal limb pain and burning pains ¹³⁰		Case series reported benefit in patients with paroxysmal limb pain and burning pains ¹³⁰		
Tricyclic antidepressants				Reported in a number of reviews to be effective. ^{103,134,135} No research studies specifically addressing this issue identified				
Steroids			Reviews report that pain associated with optic neuritis respond to steroid treatment. ^{103,135} Effect of steroids on pain not reported in the optic neuritis treatment trial ¹³⁷					

continued

TABLE 23 Drug treatments for pain syndromes in MS (cont'd)

Treatment	General	Trigeminal (and glossopharyngeal) neuralgia (TGN)	Lhermitte's sign	Paroxysmal limb pain	Optic neuritis	Dysaesthetic limb pain	Thalamic pain	Painful spasms
Baclofen		DB RCT of use in <i>idiopathic</i> TGN reported it to be effective. ¹³⁸ Also reported to have been used in MS-related TGN, but outcome not stated ¹¹⁹						Effective in the treatment of spasticity, thus reducing pain ²²
Intrathecal baclofen							Small RCT ¹¹³ and single case report ¹³⁹ showed it to be effective in suppressing dysaesthetic pain and spasticity	Effective treatment for spasticity, and hence spasticity related pain
Amantadine	4 out of 5 patients with 'chronic pain' (undefined) obtained relief from amantadine ¹⁴⁰							
Misoprostol		Case series of 7 patients with refractory MS-related TGN reported relief in 6 ¹⁴¹						

continued

TABLE 23 Drug treatments for pain syndromes in MS (cont'd)

Treatment	General	Trigeminal (and glossopharyngeal) neuralgia (TGN)	Lhermitte's sign	Paroxysmal limb pain	Optic neuritis	Dysaesthetic limb pain	Thalamic pain	Painful spasms
Octreotide						1 patient with MS reported as having pain relieved by intrathecal octreotide		
Bupivacaine						Single case report of effective treatment ¹⁴³		
Acetazolamide				Case series of 9 patients describes it as being effective in reducing painful spasms ¹⁴⁴				Reported to have reduced painful spasms in 3 patients ¹⁴⁵
Lidocaine			Complete relief in 10/12 patients ¹⁴⁷	Complete relief in 7/7 patients ¹⁴⁷				Complete relief in 10/10 patients ¹⁴⁷
Mexiletine			Partial relief only in 2/12, no relief in 10/10 patients ¹⁴⁷	Complete relief in 7/7 patients ¹⁴⁷			Case series of 9 patients with thalamic pain reported benefit – but the single patient with MS had no relief ¹⁴⁸	Complete relief in 10/10 patients ¹⁴⁷

in patients with MS induced trigeminal neuralgia has been observed.¹¹⁹ The drug has also been reported as being effective at controlling pain in three patients with glossopharyngeal neuralgia secondary to MS, and patients with 'painful tonic seizures'¹²⁰ and other paroxysmal pain syndromes.^{121,122} It has also been reported as being effective in suppressing Lhermitte's sign.¹²³ The dose used is usually 400–600 mg daily, although sometimes up to 1200 mg daily.

The use of this drug is often limited by side-effects.¹¹⁹ Further, it has been reported as being ineffective in some patients with pain associated with MS,¹²⁴ and as leading to worsening of other symptoms of MS.^{125,126}

Phenytoin

Phenytoin is an anticonvulsant licensed for control of tonic–clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. It is recommended for the treatment of trigeminal neuralgia only as second-line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.

Phenytoin is referred to as an alternative or adjunct to carbamazepine for the treatment of paroxysmal pain in MS. Again, no RCTs have been identified which have examined its effectiveness. Reviews^{115,116} suggest that it is not as consistently effective at suppressing (idiopathic) trigeminal neuralgia as is carbamazepine. There are case reports suggesting that it is effective in the treatment of painful tonic seizures¹²⁰ and non-specific limb pain.¹⁰³ Common dosage is 300 mg daily. Again, treatment may be limited by side-effects.

Gabapentin

Gabapentin is an antiepileptic drug indicated as add-on therapy for partial seizures and partial seizures with secondary generalisation in patients who have not achieved satisfactory control with, or who are intolerant to, standard anticonvulsants used alone or in combination.

Two open-label, uncontrolled studies suggest that gabapentin is effective in treating a wide variety of pain syndromes in MS.^{48,114} One reports its use, in doses up to 1.2 g daily, in 21 MS patients with paroxysmal symptoms.⁴⁸ Of these, six had trigeminal neuralgia (in whom treatment with carbamazepine or phenytoin had been tried and abandoned), and 11 had painful tonic spasms. In

all but one patient with painful spasms who dropped out, there was significant relief of symptoms. In the second,¹¹⁴ 25 MS patients with both acute and chronic pain syndromes were treated with gabapentin at doses up to 2.4 g per day (average 600 mg). 'Excellent' to 'moderate' relief of pain was reported in 15 patients, and it was observed to be more likely to be effective in those in whom the pain was described as throbbing or cramping, or pins and needles.

A case series of seven patients with trigeminal neuralgia associated with MS which was unresponsive to carbamazepine reports that six of the seven had complete, and the seventh partial, relief of pain with gabapentin.¹²⁷

A single paper¹²⁸ reports two small case series in which gabapentin was added to either carbamazepine or lamotrigine (see below) when the use of these drugs in the treatment of trigeminal neuralgia associated with MS was limited by adverse effects. In five of six patients treated with a carbamazepine–gabapentin combination there was complete amelioration of the pain, and a reduction in adverse effects following reduction in carbamazepine dosage. In five patients treated with lamotrigine–gabapentin combination there was complete pain relief, and adverse effects resolved in four of the five with reduction in lamotrigine dosage.

Two RCTs of gabapentin for the treatment of spasticity in patients with MS have shown it to be effective at reducing the frequency of painful spasms.^{50,51} A single case report describes it as ameliorating refractory dysaesthetic limb pain in MS.¹²⁹ Doses used were usually 900–1200 mg daily, occasionally up to 2400 mg daily.

Lamotrigine

Lamotrigine is an anticonvulsant licensed for use in mono- or add-on therapy for simple and complex partial seizures, and primary or secondarily generalised tonic–clonic seizures.

A case series of 21 patients with painful phenomena in MS reported that eight out of 15 patients with paroxysmal limb pain or burning pain experienced a sustained reduction in pain when treated with lamotrigine. In the same report, five of eight patients with painful spasms also reported benefit.¹³⁰ There is another case report of the effectiveness of lamotrigine in the treatment of burning pain.¹³¹

There are two reports (both unblinded case series) of the use of lamotrigine in the treatment of

trigeminal neuralgia secondary to MS. In one, all of five patients achieved complete relief with lamotrigine which lasted for at least 3 months.¹³² In the second, pain relief was achieved in 16 out of 18 patients.¹³³ Typically, doses used were up to 400 mg daily. (These two reports are from the same authors, so there may be overlap in the patients included.)

Tricyclic antidepressants

Tricyclic antidepressants, particularly amitriptyline, are reported in a number of reviews to be effective in the treatment of dysaesthetic limb pain,^{103,134,135} although not invariably so.¹³⁶ No reports of trials, or even case series, were identified which reported specifically on their effectiveness, although one is said to have been conducted.

Steroids and adrenocorticotrophin (ACTH)

Both ACTH and steroids are widely used to treat exacerbations of MS, including episodes of optic neuritis. Optic neuritis is associated with pain in the majority of cases. Reviews^{103,135} report that pain associated with optic neuritis, and a variety of other pain syndromes in MS, respond to steroid treatment.

The optic neuritis treatment trial¹³⁷ examined the effect of oral prednisolone, intravenous methylprednisolone and placebo on acute episodes of optic neuritis; 92% of patients had ocular pain at baseline. Patients treated with intravenous methylprednisolone had more rapid recovery of visual function (improved function at 2 weeks, but not maintained at 6 months) than either oral prednisolone or placebo. The effect on ocular pain is not reported.

Baclofen and intrathecal baclofen

Baclofen (both oral and intrathecal) is primarily used in MS as a treatment for spasticity (see above). Effective treatment of the spasticity will relieve any associated pain.²² Baclofen is reported to have been used in the treatment of trigeminal neuralgia in MS¹¹⁹ (though the outcome was not reported). A DB trial of its use in idiopathic trigeminal neuralgia (dose: 60–80 mg daily) reported it to be effective in reducing the number of painful paroxysms in seven out of 10 patients.¹³⁸

Intrathecal baclofen provides effective relief of spasticity with a reduced risk of side-effects as compared with oral baclofen. Again, the effective relief of spasticity will reduce associated pain. One small (seven patients, four of whom had MS) DB controlled trial of the effect of baclofen intrathecally

(bolus doses of 50 µg) has shown it to suppress both dysaesthetic pain and spasm-related pain.¹¹³ A single case report describes intrathecal baclofen as being effective in providing complete relief of dysaesthetic leg pain in a woman with MS that had previously been unresponsive to carbamazepine, amitriptyline, clonidine, mexiletine, haloperidol and oral morphine.¹³⁹

Amantidine

Amantidine is a drug used for the prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus. It has dopaminergic properties and is also used in the treatment of Parkinson's disease and for the treatment of fatigue in MS.

One letter¹⁴⁰ reports that five out of seven patients with MS who had chronic pain (nature undefined) had relief when treated with amantidine, at a dose of 2–300 mg daily. No correlation was observed between the efficacy for relief of pain (and fatigue) and the nature of the pain.

Misoprostol

Misoprostol (Cytotec) is indicated for the healing of duodenal ulcer, and gastric ulcer including those induced by non-steroidal anti-inflammatory drugs (NSAIDs) in arthritic patients at risk, whilst continuing their NSAID therapy.

A case series of seven patients with trigeminal neuralgia associated with MS who had had unsatisfactory pain relief with conventional therapy (including surgery) were treated with misoprostol.¹⁴¹ Complete pain relief was reported to have occurred in four, and partial relief in two others, using up to 200 µg four times daily.

Octreotide (intrathecal)

Octreotide is a somatostatin analogue which is used (orally) for the relief of symptoms associated with gastroenteropancreatic endocrine tumours, including carcinoid tumours with features of carcinoid syndrome, VIPomas and glucagonomas. It is also used for symptomatic control and reduction of growth hormone and somatomedin C plasma levels in patients with acromegaly.

A single report of two cases of chronic pain treated with intrathecal octreotide included one with MS.¹⁴² The patient suffered burning and tingling pains in the legs, which had not been relieved by a variety of treatments. Intrathecal octreotide, at a dose of 20 µg/hour, was associated with relief of pain, reduced supplemental opioid intake and increased activity.

Bupivacaine (intrathecal)

Bupivacaine is a local anaesthetic used for pain relief.

There is a single case report of the use of intrathecal bupivacaine in the treatment of 'refractory' pain and spasticity in a woman with MS.¹⁴³ The pains were described as stabbing, cutting, cramping and unbearable. A variety of treatments had been tried previously. With treatment at up to 95 mg/day, pain was almost completely relieved, as was spasticity, so that it was possible for the patient to sit in a wheelchair.

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor. It is indicated in the treatment of glaucoma, fluid retention (it has diuretic properties) and epilepsy, in conjunction with other anticonvulsants.

Acetazolamide has been reported to be effective in suppressing paroxysmal pain in MS. An uncontrolled case series reports it to have been effective in suppressing paroxysmal disturbances in nine patients, and details of five of them are given.¹⁴⁴ Of these, three had a painful element to the spasms. Relief from the spasms (and pain) is reported to have occurred in all three when treated with acetazolamide 750 mg daily. Another study also reported it to have abolished painful spasms in three patients.¹⁴⁵

Morphine (intrathecal)

One woman with MS and 'severe leg spasms and leg pain' is included in a case series of 43 patients with intractable pain treated with intrathecal morphine. An 'excellent' response to treatment is reported.¹⁴⁶

Lidocaine and mexiletine

Lidocaine and mexiletine are anti-arrhythmic drugs used in the treatment of ventricular arrhythmias. A single-blind, placebo-controlled study of the use of intravenous lidocaine (Xylocaine) and oral mexiletine in patients with MS reported lidocaine to be effective in the treatment of painful tonic seizures (10 of 10 patients), Lhermitte's sign (10 of 12 patients) and paroxysmal pain and itching (10 of 10 patients). Mexiletine was reportedly effective in the treatment of painful tonic seizures and paroxysmal pain, but not Lhermitte's sign.¹⁴⁷

On the other hand, in an open-label trial in patients with the thalamic pain syndrome (nine patients, of whom one had thalamic pain secondary to MS), although six of the nine were reported as having 'dramatic relief of pain' on

300 mg/day of the drug, and two 'near complete relief', the one patient with MS had no relief.¹⁴⁸

Other treatments for pain in MS

A variety of non-pharmacological approaches to the treatment of pain in MS have been reported in the literature. There is in particular a substantial body of literature on the benefit of microvascular decompression in trigeminal neuralgia, neurolysis, spinal cord stimulation, TENS and thalamotomy. Non-surgical approaches which have been reported include electromagnetic field stimulation, hypnosis and other psychological treatments. These are not within the scope of this review.

Discussion

Pain has a variety of manifestations in MS. It is clearly a common symptom, with reported prevalence of between 29 and 86% of patients. In a substantial proportion of these, it is a significant problem, being described as one of the worst of their symptoms, and interfering to a large degree with daily living.

Despite this, there is a lack of research evidence on the effectiveness of drugs to treat pain in MS. Although this review identified 14 different drugs, or groups of drugs, which have been used to treat pain in MS, some of which are well established in clinical use, it was not possible to identify a single RCT which looked specifically at the effectiveness of a drug in the treatment of pain in this condition. The majority of studies identified were either case reports or case series.

The lack of good-quality research into the treatment of pain in MS should not be taken to imply that there are not effective treatments available. Indeed, it may be the case that research into the well established treatments (carbamazepine for trigeminal neuralgia, for example) would be considered unnecessary or unethical by clinicians because they are not in a state of 'equipoise' regarding its effectiveness. However, where there are established treatments, there is scope for comparative studies. Further, unless trials are conducted of the newer treatments above while there is still clinical equipoise about their effectiveness, the opportunity to define their place in treatment will have been missed.

It is unlikely that effective interventions will be applied consistently in the absence of robust

research-based data to support them. This is evidenced by the report from the MS Society survey,³ and anecdotal information, to the effect that only a very small minority of MS patients with pain are able to access specialist treatment. It is then unsurprising that many patients seek alternative 'complementary' therapies, often at their own expense.

Conclusions

There is a great need for robust research to be undertaken into the effectiveness, and

comparative effectiveness, of different drug treatments in the treatment of pain in MS. Although some drugs are well established in current clinical use, it is not possible to be confident that they are the best that are available.

There is anecdotal evidence to the effect that access to specialist treatment for pain is variable. It is very likely, therefore, that many patients are not receiving treatment which might be of benefit to them.

Chapter 8

Implications for future research

Many of the studies included in this review are of poor quality, some achieving Jadad scores of ≤ 2 . A number of the studies are based on very small sample sizes in single sites, and are often uncontrolled. It has been common for these studies not to use blinding, leaving them open to bias. A wide variety of outcome measures have been used and even where researchers have purported to use the same instrument there have been inconsistencies in the way in which they have been used and analysed. This has made a meta-analysis impossible. More research is needed into the definition of standard outcome measures for classifying levels of spasticity in order to support comparisons between studies, and to allow definition of the different roles of the different available treatments.

Clearly, there is an urgent need for adequately powered, probably multi-centre, DB RCTs in the treatment of spasticity. This would be feasible to achieve with oral medications but it may be more difficult in relation to invasive treatments, such as intrathecal baclofen. Placebo arms may be regarded as unethical and even where placebos are used they can be easy to detect owing to the distinctive side-effects associated with some of the treatments. One way forward may be to commission more crossover studies which would allow all participants to access the intervention arm and have the added benefit of requiring fewer patients than a parallel design. This would make the introduction of a placebo arm slightly more acceptable.

The duration of some of the studies has been too short and there is a need to ensure that any future studies are of sufficient duration.

These requirements for future research are echoed by the recent Cochrane review of anti-spasticity agents for MS.⁸ Shakespeare and colleagues⁸ suggest that there are serious problems in understanding and measuring spasticity and that the wide variety of approaches taken to measure it reflect this confusion. The Ashworth scale is interpreted in a variety of ways and this makes comparison between studies problematic. Likewise, there are problems with the definition of weakness which may have different meanings in different studies. There is a requirement to develop more meaningful instruments to measure spasticity which have some correlation with the patient's experience and QoL.

There is a remarkable lack of good-quality research into the effectiveness of drugs to treat pain in MS. The majority of studies identified were either case reports or case series. Although this does not mean that the various treatments currently in common use are not effective, it does make it unlikely that effective treatments will be in uniform use throughout the NHS (and there is evidence that they are not). It also means that the relative effectiveness of the available drugs in different circumstances is not established.

Finally, there is lack of evidence for the role of non-drug therapy for spasticity and pain in MS and this also needs to be addressed by the development of large-scale, pragmatic RCTs.



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Appendix I

Jadad scale for assessing the quality of published research

The criteria included in the Jadad scale are as follows:

1. Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?
2. Was the study described as double blind?
3. Was there a description of the withdrawals and dropouts?

Give a score of one point for each 'yes' or no points for 'no'.

Give one additional point if the method to generate the sequence of randomisation was described and was appropriate (table of random numbers, computer-generated, etc.). Deduct one point if this method was inappropriate (patients allocated alternately, according to date of birth, hospital number, etc.).

Give one point if the study was described as double blind, but the method of blinding was appropriate (identical placebo, active placebo, dummy, etc.). Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet versus injection with no double dummy).

Participants who were included in the study, but did not complete the observation period or who were not included in the analysis, must be described. The number and reasons for each withdrawal must be stated. If there were no withdrawals, it should also be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Appendix 2

Outcome measures and rating scales

Ashworth scale

The Ashworth scale (*Table 24*) is an ordinal scale which usually ranges from 0 to 4. However, some of the papers in this review use the same categories ranging from 1 to 5. There seems to be some confusion amongst researchers as to the difference between the Ashworth scale and the modified version and it would appear that some researchers use the two terms interchangeably. Both the original scale and the modified version have been shown to have good inter-rater reliability.^{151,152}

As the Ashworth scale is an ordinal scale, rather than a ratio or interval scale, it is inappropriate to summate and calculate the mean of Ashworth scores in different muscle groups or different patients (as most investigators do). Rather, non-parametric statistical methods should be used to analyse results.

The main problem with the Ashworth scale is that a change in the score does not necessarily correlate with a change in the patient's function or QoL.

British Medical Research Council for Muscle Strength (BMRC scale)

- 5 = normal muscle strength
- 4.5 = voluntary movement against major resistance applied by examiner but not normal
- 4 = voluntary movement against moderate resistance applied by examiner
- 3.5 = voluntary movement against mild resistance applied by examiner
- 3 = voluntary movement present, but not able to overcome gravity
- 1 = contraction of muscle visible or detected by palpation, but without effect in the limb
- 0 = absence of any voluntary movement

TABLE 24 Ashworth scale for assessment of muscle tone (*hypertonia scale*)

Ashworth scale ⁶¹		Modified Ashworth scale ¹⁵⁰	
Score	Meaning	Score	Meaning
0	No increase in tone	0	No increase in tone
1	Slight increase in tone giving a 'catch' when the limb is moved in flexion or extension	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
–	–	2	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in tone but limb easily flexed	3	More marked increase in muscle tone through most of the range of motion, but affected part(s) easily flexed
3	Considerable increase in tone, passive movement difficult	4	Considerable increase in tone, passive movement difficult
4	Limb rigid in flexion or extension	5	Affected part(s) rigid in flexion or extension

Penn Frequency of Spasm scale

Grade	Clinical condition
0	None
1	No spontaneous spasms/spasms induced by stimulation
2	Occasional spontaneous spasms and easily induced spasms
3	> 1, but < 10, spontaneous spasms per hour
4	> 10 spontaneous spasms per hour

Oxford Scale for muscle strength

Grade	Clinical condition
1	Normal
2	Movement against slight resistance
3	Movement against gravity
4	Slight movement against gravity
5	Isometric contractions only
6	Paralysis

Wartenburg pendulum test (amplitude of first knee-swing)

The pendulum test was developed in 1951 by Wartenburg as a measure of change in resting muscle tone.

QoL measures

Sickness Impact Profile (SIP)

The SIP is a general health status measure which consists of 12 categories.¹⁵³ The SIP produces a score for each of the physical and psychosocial dimensions and also an overall score. A low score represents minimal impairment and a high score represents increasing disability.

Kurtzke Expanded Disability Status Scale (EDSS)

The EDSS is a 20-point scale proposed in 1983 by Kurtzke and is based on the Disability Status Scale (DSS), a 10-point scale by the same author.¹⁵⁴ It has been widely used as a tool to measure disability and overall function in MS. The global rating scores range from 0 to 10; moving from a normal score of 0 through various signs and symptoms and ending in death with a score of 10. The EDSS divides the DSS between break points 1–9 (inclusive) into half points. The EDSS has been substantially criticised; in particular, there is concern that a change in score does not necessarily reflect a clinically significant change. The EDSS focuses mainly on mobility and neglects other types of impairment, such as blindness or dementia.

Appendix 3

Search strategies

Scoping review

MEDLINE search strategies (OVID BIOMED 1966–)

Initial scoping search

- 1 Multiple sclerosis/
- 2 exp Pain/
- 3 Pain measurement/
- 4 Muscle spasticity/
- 5 Spasm/
- 6 2 or 3 or 4 or 5
- 7 1 and 6

Multiple sclerosis and pain

- 1 exp multiple sclerosis/
- 2 "multiple sclerosis".tw.
- 3 "disseminated sclerosis".tw.
- 4 or/1-3
- 5 exp pain/
- 6 pain\$.tw.
- 7 or/4-6
- 8 exp Thalamic diseases/
- 9 exp Thalamus/
- 10 thalam\$.tw.
- 11 or/8-10
- 12 7 and 11
- 13 4 and 12
- 14 limit 13 to english language
- 15 exp Optic neuritis/
- 16 (optic or eye).tw.
- 17 or/15-16
- 18 7 and 17
- 19 4 and 18
- 20 limit 19 to english language
- 21 exp Trigeminal neuralgia/
- 22 7 and 21
- 23 4 and 22
- 24 limit 23 to english language
- 25 ((dysaesthe\$ or dysesthe\$) adj5 limb\$).tw.
- 26 (dysaesthesia or dysesthesia).tw.
- 27 or/25-26
- 28 7 and 27
- 29 4 and 28
- 30 limit 29 to english language
- 31 (paroxysmal\$ adj5 limb\$).tw.
- 32 7 and 31
- 33 4 and 32
- 34 limit 33 to english language/
- 35 exp Spinal nerve roots/
- 36 ((nerve\$ or neuron\$) adj5 root\$).tw.

- 37 or/35-36
- 38 7 and 37
- 39 4 and 38
- 40 limit 39 to english language
- 41 "lhermitte\$ sign".tw.
- 42 7 and 41
- 43 4 and 42
- 44 limit 43 to english language
- 45 exp Musculoskeletal physiology/
- 46 postur\$.tw.
- 47 or/45-46
- 48 7 and 47
- 49 4 and 48
- 50 limit 49 to english language
- 51 meta-analysis/
- 52 exp review literature/
- 53 (meta-analy\$ or meta analy\$ or metaanaly\$).tw.
- 54 meta analysis.pt.
- 55 review academic.pt.
- 56 review literature.pt.
- 57 letter.pt.
- 58 review of reported cases.pt.
- 59 historical article.pt.
- 60 review multicase.pt.
- 61 or/51-56
- 62 or/57-60
- 63 61 not 62
- 64 19 and 63
- 65 limit 64 to english language
- 66 49 and 63
- 67 limit 66 to english language
- 68 randomized controlled trial.pt.
- 69 controlled clinical trial.pt.
- 70 randomized controlled trials/
- 71 random allocation/
- 72 double blind method/
- 73 single blind method/
- 74 or/68-73
- 75 clinical trial.pt.
- 76 exp clinical trials/
- 77 (clin\$ adj25 trial\$).ti,ab.
- 78 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
- 79 placebos/
- 80 placebos.ti,ab.
- 81 random.ti,ab.
- 82 research design/
- 83 or/75-82
- 84 comparative study/

85 exp evaluation studies/
 86 follow up studies/
 87 (control\$ or prospectiv\$ or
 volunteer\$).ti,ab.
 88 prospective studies/
 89 or/84-88
 90 74 or 83 or 89
 91 19 and 90
 92 limit 91 to english language
 93 49 and 90
 94 limit 93 to english language

Multiple sclerosis and pain treatments


1 exp multiple sclerosis/
 2 "multiple sclerosis".tw.
 3 "disseminated sclerosis".tw.
 4 or/1-3
 5 exp pain/
 6 pain\$.tw.
 7 or/4-6
 8 exp Thalamic diseases/
 9 exp Thalamus/
 10 thalam\$.tw.
 11 or/8-10
 12 7 and 11
 13 4 and 12
 14 limit 13 to english language
 15 exp Optic neuritis/
 16 (optic or eye).tw.
 17 or/15-16
 18 7 and 17
 19 4 and 18
 20 limit 19 to english language
 21 exp Trigeminal neuralgia/
 22 7 and 21
 23 4 and 22
 24 limit 23 to english language
 25 ((dysaesthe\$ or dysesthe\$) adj5 limb\$).tw.
 26 (dysaesthesia or dysesthesia).tw.
 27 or/25-26
 28 7 and 27
 29 4 and 28
 30 limit 29 to english language
 31 (paroxysmal\$ adj5 limb\$).tw.
 32 7 and 31
 33 4 and 32
 34 limit 33 to english language
 35 exp Spinal nerve roots/
 36 ((nerve\$ or neuron\$) adj5 root\$).tw.
 37 or/35-36
 38 7 and 37
 39 4 and 38
 40 limit 39 to english language
 41 "lhermitte\$ sign".tw.
 42 7 and 41
 43 4 and 42
 44 limit 43 to english language

45 exp Musculoskeletal physiology/
 46 postur\$.tw.
 47 or/45-46
 48 7 and 47
 49 4 and 48
 50 limit 49 to english language
 51 meta-analysis/
 52 exp review literature/
 53 (meta-analy\$ or meta analy\$ or
 metaanaly\$).tw.
 54 meta analysis.pt.
 55 review academic.pt.
 56 review literature.pt.
 57 letter.pt.
 58 review of reported cases.pt.
 59 historical article.pt.
 60 review multicase.pt.
 61 or/51-56
 62 or/57-60
 63 61 not 62
 64 19 and 63
 65 limit 64 to english language
 66 49 and 63
 67 limit 66 to english language
 68 randomized controlled trial.pt.
 69 controlled clinical trial.pt.
 70 randomized controlled trials/
 71 random allocation/
 72 double blind method/
 73 single blind method/
 74 or/68-73
 75 clinical trial.pt.
 76 exp clinical trials/
 77 (clin\$ adj25 trial\$).ti,ab.
 78 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25
 (blind\$ or mask\$)).ti,ab.
 79 placebos/
 80 placebos.ti,ab.
 81 random.ti,ab.
 82 research design/
 83 or/75-82
 84 comparative study/
 85 exp evaluation studies/
 86 follow up studies/
 87 (control\$ or prospectiv\$ or
 volunteer\$).ti,ab.
 88 prospective studies/
 89 or/84-88
 90 74 or 83 or 89
 91 19 and 90
 92 limit 91 to english language
 93 49 and 90
 94 limit 93 to english language
 95 12 or 18 or 22 or 28 or 32 or 38 or 42 or
 48
 96 exp Antidepressive agents, tricyclic/
 97 exp Anticonvulsants/

- 98 carbamazepine.tw.
 99 carbamazepine.rn.
 100 carbamazepine.rw.
 101 carbamazepine/
 102 or/97-101
 103 exp Phenytoin/
 104 phenytoin.tw.
 105 phenytoin.rn.
 106 phenytoin.rw.
 107 or/103-106
 108 exp baclofen/
 109 baclofen.tw.
 110 baclofen.rn.
 111 baclofen.rw.
 112 or/108-111
 113 exp Misoprostol/
 114 misoprostol.tw.
 115 misoprostol.rn.
 116 misoprostol.rw.
 117 or/113-116
 118 exp Analgesics/
 119 Steroids/
 120 gabapentin.tw.
 121 gabapentin.rn.
 122 gabapentin.rw.
 123 or/120-122
 124 exp Transcutaneous electric nerve
 stimulation/
 125 ("spinal cord\$" or "dorsal column\$") adj5
 stimulat\$.tw.
 126 96 or 102 or 107 or 112 or 117 or 118 or
 119 or 123 or 124 or 125
 127 lamotrigine.tw.
 128 lamictal.tw.
 129 lamiktal.tw.
 130 lamotrigine.rn.
 131 lamotrigine.rw.
 132 or/127-131
 133 96 or 102 or 107 or 112 or 117 or 118 or
 119 or 123 or 124 or 125 or 132
 134 95 and 133
 135 4 and 134
 136 limit 135 to english language
- Multiple sclerosis and treatments for spasticity
 (two strategies)**
- 1 exp Multiple sclerosis/
 2 multiple sclerosis.tw.
 3 multiple sclerosis.in.
 4 (disseminat\$ adj3 sclerosis).tw.
 5 multiple sclerosis.jw.
 6 multiple sclerotic.tw.
 7 or/1-6
 8 exp Botulinum toxins/
 9 botulinum toxin\$.tw.
 10 botulinum toxin\$.rw.
 11 botox.tw.
- 12 dysport.tw.
 13 or/8-12
 14 exp diazepam/
 15 diazepam.tw.
 16 diazepam.rw.
 17 439 14 5.rn.
 18 or/14-17
 19 dantrolene/
 20 dantrolene.tw.
 21 dantrolene.rw.
 22 dantrium.tw.
 23 7261 97 4.rn.
 24 or/19-23
 25 tizanidine.tw.
 26 zanaflex.tw.
 27 tizanidine.rw.
 28 51322 75 9.rn.
 29 or/25-28
 30 baclofen/
 31 baclofen.tw.
 32 "1134 47 0".rn.
 33 baclofen.rw.
 34 or/30-33
 35 exp Methylprednisolone/
 36 methylprednisolone.tw.
 37 methylprednisolone.rw.
 38 83 43 2.rn.
 39 solumedrone.tw.
 40 depomedrone.tw.
 41 or/35-40
 42 exp Threonine/
 43 threonine.rw.
 44 threonine.tw.
 45 72 19 5.rn.
 46 or/42-45
 47 Vigabatrin/
 48 vigabatrin.tw.
 49 vigabatrin.rw.
 50 60643 86 9.rn.
 51 sabril.tw.
 52 or/47-51
 53 Clonidine/
 54 clonidine.tw.
 55 clonidine.rw.
 56 4205 90 7.rn.
 57 catapres.tw.
 58 dixarit.tw.
 59 or/53-58
 60 Mexiletine/
 61 mexiletine.tw.
 62 mexiletine.rw.
 63 31828 71 4.rn.
 64 mexitil.tw.
 65 or/60-64
 66 13 or 18 or 24 or 29 or 34 or 41 or 46 or
 52 or 59 or 65
 67 7 and 66

- 68 randomized controlled trial.pt.
69 controlled clinical trial.pt.
70 Randomized controlled trials/
71 Random allocation/
72 Double-blind method/
73 Single-blind method/
74 or/68-73
75 clinical trial.pt.
76 exp Clinical trials/
77 (clin\$ adj25 trial\$).tw.
78 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25
(blind\$ or mask\$)).tw.
79 Placebos/
80 placebo\$.tw.
81 random\$.tw.
82 Research design/
83 or/75-82
84 "comparative study"/
85 exp evaluation studies/
86 Follow-up studies/
87 Prospective studies/
88 (control\$ or prospectiv\$ or
volunteer\$).tw.
89 or/84-88
90 74 or 83 or 89
91 "animal"/
92 "human"/
93 91 not 92
94 90 not 93
95 Meta-analysis/
96 exp review literature/
97 (meta analy\$ or metaanaly\$).tw.
98 meta analysis.pt.
99 review academic.pt.
100 review literature.pt.
101 letter.pt.
102 review of reported cases.pt.
103 historical article.pt.
104 review multicase.pt.
105 or/95-100
106 or/101-104
107 105 not 106
108 "human"/
109 "animal"/
110 109 not 108
111 107 not 110
112 107 not 111
113 Economics/
114 exp "Costs and cost analysis"/
115 Economic value of life/
116 exp Economics, hospital/
117 exp Economics, medical/
118 Economics, nursing/
119 exp models, economic/
120 Economics, pharmaceutical/
121 exp "Fees and charges"/
122 exp Budgets/
123 ec.fs.
124 (cost or costs or costed or costly or
costing\$).tw.
125 (economic\$ or pharmacoeconomic\$ or
price\$ or pricing).tw.
126 Quality-adjusted life years/
127 or/113-126
128 67 and 94
129 67 and 111
130 67 and 127
131 128 or 129 or 130
1 exp Benzodiazepines/
2 benzodiazepine\$.tw,rw.
3 benzodiazepinone\$.tw,rw.
4 alprazolam.tw,rw.
5 chlordiazepoxide.tw,rw.
6 clorazepate dipotassium.tw,rw.
7 estazolam.tw,rw.
8 medazepam.tw,rw.
9 midazolam.rw,tw.
10 triazolam.tw,rw.
11 anthramycin.tw,rw.
12 bromazepam.tw,rw.
13 clonazepam.tw,rw.
14 devazepide.tw,rw.
15 flumazenil.tw,rw.
16 flunitrazepam.tw,rw.
17 flurazepam.tw,rw.
18 lorazepam.tw,rw.
19 nitrazepam.tw,rw.
20 oxazepam.tw,rw.
21 pirenzepine.tw,rw.
22 prazepam.tw,rw.
23 temazepam.tw,rw.
24 28981 97 7.rn.
25 58 25 3.rn.
26 57109 90 7.rn.
27 29975 16 4.rn.
28 2898 12 6.rn.
29 59467 70 8.rn.
30 "28911 01 5".rn.
31 4803 27 4.rn.
32 1812 30 2.rn.
33 1622 61 3.rn.
34 103420 77 5.rn.
35 78755 81 4.rn.
36 1622 62 4.rn.
37 17617 23 1.rn.
38 846 49 1.rn.
39 146 22 5.rn.
40 604 75 1.rn.
41 28797 61 7.rn.
42 2955 38 6.rn.
43 846 50 4.rn.
44 hypnovel.tw.
45 rohypnol.tw.

46	dalmane.tw.	87	"animal"/
47	loprazolam.tw.	88	"human"/
48	lormetazepam.tw.	89	87 not 88
49	or/1-48	90	86 not 89
50	exp Multiple sclerosis/	91	Meta-analysis/
51	multiple sclerosis.tw.	92	exp review literature/
52	multiple sclerosis.in.	93	(meta analy\$ or metaanaly\$).tw.
53	(disseminat\$ adj3 sclerosis).tw.	94	meta analysis.pt.
54	multiple sclerosis.jw.	95	review academic.pt.
55	multiple sclerotic.tw.	96	review literature.pt.
56	or/50-55	97	letter.pt.
57	49 and 56	98	review of reported cases.pt.
58	exp diazepam/	99	historical article.pt.
59	diazepam.tw.	100	review multicase.pt.
60	diazepam.rw.	101	or/91-96
61	439 14 5.rn.	102	or/97-100
62	or/58-61	103	101 not 102
63	57 not 62	104	"human"/
64	randomized controlled trial.pt.	105	"animal"/
65	controlled clinical trial.pt.	106	105 not 104
66	Randomized controlled trials/	107	103 not 106
67	Random allocation/	108	Economics/
68	Double-blind method/	109	exp "Costs and cost analysis"/
69	Single-blind method/	110	Economic value of life/
70	or/64-69	111	exp Economics, hospital/
71	clinical trial.pt.	112	exp Economics, medical/
72	exp Clinical trials/	113	Economics, nursing/
73	(clin\$ adj25 trial\$).tw.	114	exp models, economic/
74	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw.	115	Economics, pharmaceutical/
75	Placebos/	116	exp "Fees and charges"/
76	placebo\$.tw.	117	exp Budgets/
77	random\$.tw.	118	ec.fs.
78	Research design/	119	(cost or costs or costed or costly or costing\$).tw.
79	or/71-78	120	(economic\$ or pharmaco-economic\$ or price\$ or pricing).tw.
80	"comparative study"/	121	Quality-adjusted life years/
81	exp evaluation studies/	122	or/108-121
82	Follow-up studies/	123	63 and 90
83	Prospective studies/	124	63 and 107
84	(control\$ or prospectiv\$ or volunteer\$).tw.	125	63 and 122
85	or/80-84	126	123 or 124 or 125
86	70 or 79 or 85		



Health Technology Assessment Programme

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We look forward to hearing from you.