National Institute for Health and Care Excellence

Draft

Multiple sclerosis in adults: management (update)

[F] Evidence review for pharmacological management of spasticity

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.20 to 1.5.28 and research recommendations in the NICE guideline

December 2021

Draft for Consultation

These evidence reviews were developed by National Guideline Centre, hosted by Royal College of Physicians

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Pharmacological management of spasticity

1.1 Review question

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of pharmacological interventions for spasticity?

1.1.1 Introduction

Spasticity is a common problem in multiple sclerosis, affecting up to 80% of people with the diagnosis. The nature, symptoms and consequences of spasticity can vary significantly between people and can change over the course of the disease. It is important to assess and treat each individual according to the particular effects that spasticity may have on participation, function and quality of life. Assessment and treatment is delivered through multidisciplinary teams experienced in the management of spasticity (including a Consultant in Rehabilitation Medicine).

There are many different approaches that may be adopted according to the particular needs of the individual. This part of the guideline gives a basic overview of the issues that need to be considered in the approach to a person with MS and spasticity and the importance of holistic multidisciplinary assessment and treatment. Basic guidance around initiation of systemic pharmacological therapies is described. Suggested onwards referral to specialist rehabilitation services for focal treatments (botulinum toxin and intrathecal baclofen) or complex pharmacological management (including cannabis-derived medication) where this is appropriate has been highlighted.

This review focuses on the pharmacological management of spasticity as this is the area where the surveillance report suggested there may be sufficient new evidence since the last guideline (2014) to warrant updating the evidence review.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (≥18 years) with MS, including people receiving palliative care.
Interventions	• Baclofen (oral) (Lioresal)- used more widely • Baclofen (intrathecal) – to be kept separate to oral • Tizanidine (Zanaflex) • Gabapentin (Neurontin) • Dantrolene sodium (Dantrium) • Benzodiazepines (Diazepam, clonazepam) • Botulinum toxin (Azzalure, Bocouture, Botox, Dysport, Vistabel, Xeomin) • Pregabalin (Lyrica) • Phenol- used by injection in 2 way: intrathecal and peripheral nerve block (consider 2 separate interventions) • Combinations of the above
Comparisons	Interventions will be compared to each other (both within and between classes), to placebo/sham, or to usual care or no treatment.

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical.
	• Spasticity scales for example:
	  ○ Modified Ashworth scale
	  ○ Tardieu Scale
	  ○ Muscle Elastography MS Scale (MEMSs)
	  ○ Fugl Meyer Scale (FMS)
	• Patient reported measures of spasticity for example:
	  ○ Penn Spasm Frequency Scale
	  ○ Numeric Rating Scale for Spasticity (NRS-S)
	  ○ MS Spasticity Scale-88 (MSSS)
	  ○ Patient-reported Impact of Spasticity Measure (PRISM)
	• Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale
	• Adverse effects of treatment for example:
	  ○ Any adverse events
	  ○ Adverse events leading to withdrawal
	  ○ Drowsiness
	  ○ Weakness
	  ○ Nausea
	  ○ Mobility
	• Pain scales for example visual analogue scale (VAS)
	• Improvement in sleep
	• Comfort and posture positioning (self-reported)
	• Functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), the Functional Assessment of Multiple Sclerosis (FAMS), the National Fatigue Index (NFI) or the MS walking scale.
	• Impact on patients/ carers
	
	Follow up:
	• 3-6 months (minimum of 3 months but can include 1-3 months and downgrade)
	• >6 months – 1 year (data from >1 year follow up may be included but will be downgraded)

Study design	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion if they have an appropriate washout period which is no less than a week

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

No relevant clinical studies comparing pharmacological treatments for spasticity in people with MS were identified since the last update of the guideline.

Twenty seven studies were included in the review.[3-17, 19-24, 26, 28-32] A Cochrane review[27] was also found, but because this looked at different comparisons to those chosen for our review protocol, contained non-published studies, and also only contained studies up to 2003, we decided to extract and analyse from the primary sources only. The study characteristics are summarised in Table 37.

Ten different comparisons were covered in this review. Nine concerned orally-administered drugs, and one concerned intrathecal baclofen. The studies were:

- Oral baclofen v placebo[3, 20, 23, 24]
- Tizanidine v placebo[13, 28, 32]
- Tizanidine v oral baclofen[5, 9, 29, 30]
- Diazepam v oral baclofen[6, 22]
- Tizanidine v diazepam[21]
- Dantrolene v diazepam[26]
- Dantrolene v placebo[7, 31]
- Gabapentin v placebo[4]
- Botulinum v placebo[8, 11, 12]
- Intrathecal baclofen v placebo[10, 14-17, 19]

As stated in the protocol, all comparisons were made on a population with Multiple sclerosis, with the exception of the intrathecal baclofen evidence. The population in this study were a mixed population of acquired adult neurological disease. The decision to include a mixed population was made by the Guideline Development Group on the grounds that 1) there were no studies in a pure MS population, 2) intrathecal baclofen was a potentially important intervention that should be assessed, and 3) there were no good physiological reasons why the alternative neurological diagnoses should unduly influence the effects of the drug on spasticity.

Table 2: Summary of studies included in the review

Study	Intervention/comparison	Mean MS characteristics where available (group-specific data designated by intervention / comparator)	n	Analysis
Orsnes2000[176]	Oral baclofen v placebo	Median Ashworth 0.8 (range 0-2) Median EDSS 5	14	Cross-over
Brar1991[27]		Mild to moderate spasticity EDSS 5.5 or less	38	Cross-over
Sawa1979[213]		Ashworth 3 / 3	21	Cross-over
Sachais1997[208]		Duration of disease 11/ 11 years	166	Parallel
UKTTG1994[244]	Tizanidine v placebo	Moderate or severe spasticity: 61% / 53% Disease duration 12.7 / 13.1 years	187	Parallel
Smith1994[228]		% scoring 4 on Ashworth 22% / 23% Disease duration 10.8 / 11.2 years	256	Parallel
LaPierre1987[118]		At least “moderate” spasticity EDSS 5.07 / 5.07	66	Parallel
Hoogstraten1988[99]	Tizanidine v oral baclofen	EDSS 4-7	16	Cross-over
Eyssette1988[59]		Mean duration of MS 10.8 / 13.4 years Duration of signs 17.3 / 26.6 years	100	Parallel
Bass1988		Moderate or severe spasticity: 91% / 87%	66	Cross-over
Stien1987[238]		Moderate or severe spasticity: 78% / 90% Disease duration 14 / 13 years	40	Parallel
Smolenski1981[230]		Severe spasticity 36% / 60%	21	Parallel
Roussan1997[205]	Diazepam v baclofen	Duration of spasticity 10.8 years	6	Cross-over
From1975[69]		Duration of MS 17.5 years (range 3 – 40)	17	Parallel
Rinne1980[196]	Tizanidine v diazepam	Moderate or severe spasticity: 93% / 93% MS duration 7 / 12 years	30	Parallel
Schmidt1976[215]	Dantrolene v diazepam	Moderate or severe spasticity	46	Cross-over
Gelenberg1973[77]	Dantrolene v placebo	Moderate to severe spasticity 70% able to ambulate but with difficulty	20	Cross-over
Tolosa1975[247]		No data reported	23	Parallel

Study	Intervention/comparison	Mean MS characteristics where available (group-specific data designated by intervention / comparator)	n	Analysis
Cutter2000[48]	Gabapentin v placebo	Clinical evidence of spasticity	22	Cross-over
Hyman2000[103,104]	Botulinum v placebo	Modified Ashworth 8.5 – 16 EDSS > 7 Duration of MS 16.6 – 22.9 years	74	Parallel
Gusev2008[86]		Duration of MS 12.9 / 13.9 years	106	Parallel
Middel 1997[143]	Intrathecal baclofen v placebo	59% with MS, 41% had spinal cord injury; no other details available	22	Parallel
Meythaler 2001[142]		All with CVA, and intractable spastic hypertonia	22	Parallel
Loubser 1991[126]		All with spinal cord injury, with intractable spasticity	9	Cross-over
Hugenholtz 1992[100]		2/6 MS; others SCI. All with intractable spasticity	6	Cross-over
Ordia 1996[174]		Not reported for the subset in the RCT, but probably MS or SCI. All with intractable spasticity	9	Parallel
Meythaler 1996[141]		Brain injury patients, with intractable spasticity	11	Cross-over

See study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.5 Economic evidence

Published Literature

No relevant economic evaluations comparing pharmacological treatments for the management of spasticity were identified.

1.1.5.1 Included studies

No health economic studies were included.

1.1.5.2 Excluded studies

One relevant health economic study relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations[1]. This is listed in Appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix F.

1.1.5.3 Summary of effectiveness evidence

As discussed in section 2,8 of the methods chapter evidence from the previous (2014) guideline is presented in its originally format.

Table 3: Clinical evidence profile: baclofen versus placebo

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Self-evaluation of gait improvement (higher better)												
Orsenes2000	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	5/13 (38.5%)	4/13 (30.8%)	RR 1.25	77 more per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute(95 % CI)		
									(0.43 to 3.63)	175 fewer to 809 more)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Patients showing improvement in Ashworth scale (higher better)												
Brar1991	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	9/30 (30%)	6/30 (20%)	RR 1.5 (0.61 to 3.69)	100 more per 1000 (from 78 fewer to 538 more)	VERY LOW	CRITICAL
Detectable improvement in spasticity assessed by investigator												
Sawa 1979	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/18 (72.2%)	0/18 (0%)	Peto OR: 20.98 (5.49 to 80.21)	720 more per 1000 (from 510 more to 940 more)	MOD	CRITICAL
Physician assessment of clinical change in overall spastic state (higher better)												
Sachais 1997	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	3.02(1.03)[52]	2.37(1.03)[52]	-	MD: 0.65 more (from 0.25 more to 1.05 more)	VERY LOW	CRITICAL
Physician assessment of clinical change in daytime spasms (higher better)												

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Sachais 1997	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	2.88(1.35)[43]	2.23(1.35)[44]	-	MD: 0.65 more (from 0.08 more to 1.22 more)	VERY LOW	IMPORTANT
Physician assessment of clinical change in night-time spasms (higher better)												
Sachais 1997	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	2.85(1.14)[40]	2.29(1.14)[45]	-	MD: 0.56 more (from 0.07 more to 1.05 more)	VERY LOW	IMPORTANT
Adverse events leading to treatment withdrawal												
Sawa1979	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	1/21 (4.8%)	0/18 (0%)	Peto OR 6.41 (0.13 to 326.59)	50 more per 1000 (from 80 less to 180 more)	VERY LOW	CRITICAL
Adverse events - somnolence												
Sachais1997 Sawa1979	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/106 (62.3%)	29/102 (28.4%) 17.9%	RR 2.15 (1.56 to 2.98)	206 more per 1000 (from 100 more to 354 more)	LOW	IMPORTANT
Adverse events - weakness												
Sachais1997 Sawa1979	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	Serious[B]	none	20/106 (18.9%)	9/102 (8.8%) 5.6%	RR 2.07 (1.01 to 4.24)	60 more per 1000 (from 1 more to 181 more)	VERY LOW	IMPORTANT

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Adverse events – nausea												
Sachais1997 Sawa1979	randomised trials	very serious [A]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/106 (17.9%)	5/102 (4.9%) 3.1%	RR 3.41 (1.38 to 8.44)	75 more per 1000 (from 12 more to 231 more)	LOW	IMPORTANT

[A] *Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.*

[B] *Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.*

1 **Table 4: Clinical evidence profile: tizanidine versus placebo**

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tizanidine	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Patient assessment of efficacy - good or very good												
UKTTG1994	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	25/89 (28.1%)	13/93 (14%)	RR 2.01 (1.1 to 3.68)	141 more per 1000 (from 14 more to 375 more)	VERY LOW	CRITICAL
Patient assessment of tolerability - good or very good												
UKTTG1994	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/89 (40.4%)	79/93 (84.9%)	RR 0.48 (0.36 to 0.62)	442 fewer per 1000 (from 323 fewer to 544 fewer)	LOW	CRITICAL
Ashworth improved												
Smith1994 UKTTG1994	randomised trials	very serious[A]	Very serious[C]	no serious indirectness	serious[B]	none	131/205 (63.9%)	112/202 (55%)	Random RR 1.16 (0.8 to 1.69)	88 more per 1000 (from 110 fewer to 380 more)	VERY LOW	CRITICAL
Patients discontinuing because of adverse events												

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tizanidine	Placebo	Relative (95% CI)	Absolute(95% CI)		
UKTTG1994	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	12/94 (12.8%)	5/93 (5.4%)	RR 2.37 (0.87 to 6.47)	74 more per 1000 (from 7 fewer to 294 more)	VERY LOW	CRITICAL
Numbers with improved upper limb function (higher better)												
UKTTG1994	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	5/87 (5.7%)	4/88 (4.5%)	RR 1.26 (0.35 to 4.55)	12 more per 1000 (from 30 fewer to 161 more)	VERY LOW	IMPORTANT

[A] Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.

[B] Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.

[C]Outcomes were downgraded by one increment for serious inconsistency, as shown by the I squared value being between 50 and 74%. A double downgrade was applied for very serious inconsistency if I squared was >75%. A random effects model was used for any inconsistent outcomes. No subgrouping was applied, as all outcomes with inconsistency did not have >2 studies (and thus sub-grouping would always lead to one in each sub-group, which would inevitably reduce inconsistency to zero in each sub-group, thus making any sub-grouping non-informative).

Table 5: Clinical evidence profile: tizanidine versus baclofen

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tizanidine	Baclofen	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Spasticity worse or no better												
Hoogstraten1988	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	Ln[RR](SE): -0.223(0.387)		RR 0.80 (0.37 to 1.71)	Not available	VERY LOW	CRITICAL
Spasms worse or no better												
Hoogstraten1988	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	Ln[RR](SE): -0.693(0.527)		RR 0.50 (0.18 to 1.40)	Not available	VERY LOW	IMPORTANT
Mobility worse or no better												
Hoogstraten1988	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	Ln[RR](SE): -0.201(0.142)		RR 1.22 (0.93 to 1.61)	Not available	LOW	IMPORTANT
Overall evaluation of tolerability - patients stating treatment was poorly tolerated												
Eyssette1988	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	6/50 (12%)	4/50 (8%)	RR 1.5 (0.45 to 4.99)	40 more per 1000 (from 44 fewer to 319 more)	VERY LOW	CRITICAL

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tizanidine	Baclofen	Relative (95% CI)	Absolute(95% CI)		
Discontinuation due to adverse events												
Bass1988 Eyssette1988 Stien1987	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	11/102 (10.8%)	16/100 (16%) 8%	RR 0.66 (0.33 to 1.35)	27 fewer per 1000 (from 54 fewer to 28 more)	VERY LOW	CRITICAL
Overall assessment of patient of the efficacy (moderate/poor or "ineffective at end of study")												
Bass1988 Smolenski1981 Stien1987 Eyssette 1988	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	72/133 (54.1%)	59/131 (45%) 45.4%	RR 1.21 (0.97 to 1.49)	95 more per 1000 (from 14 fewer to 222 more)	LOW	CRITICAL
Adverse events - somnolence												
Bass1988 Hoogstraten1988 Smolenski1981	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	28/57 (49.1%)	13/54 (24.1%) 28.6%	RR 2.01 (1.18 to 3.42)	289 more per 1000 (from 51 more to 692 more)	LOW	IMPORTANT
Adverse events - nausea												
Hoogstraten1988 Smolenski1981	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	2/25 (8%)	4/24 (16.7%) 15.7%	RR 0.54 (0.13 to 2.26)	72 fewer per 1000 (from 137 fewer to 198 more)	VERY LOW	IMPORTANT
Adverse events - weakness												
Bass1988 Smolenski1981	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	13/43 (30.2%)	20/47 (42.6%) 37.2%	RR 0.66 (0.38 to 1.13)	126 fewer per 1000 (from	LOW	IMPORTANT

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tizanidine	Baclofen	Relative (95% CI)	Absolute(95 % CI)		
										231 fewer to 48 more)		

[A] *Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.*

[B] *Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.*

1 **Table 6: Clinical evidence profile: diazepam versus balcofen**

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	baclofen	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Spasticity outcomes												
No evidence available												
Better patient rated global response												
Roussan1997	randomised trials	serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	3/6 (50%)	1/6 (16.7%)	RR 3 (0.42 to 21.3)	333 more per 1000 (from 97 fewer to 1000 more)	VERY LOW	CRITICAL
Adverse events - weakness												
From1975	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	2/16 (12.5%)	3/16 (18.8%)	RR 0.67 (0.13 to 3.47)	62 fewer per 1000 (from 163 fewer to 463 more)	VERY LOW	IMPORTANT
Adverse events- somnolence												
From1975 Roussan1997	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	No serious imprecision	none	RR: 4.45(1.45 to 13.65)		RR: 4.45(1.45 to 13.65)	Not available	LOW	IMPORTANT

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	baclofen	Relative (95% CI)	Absolute(95 % CI)		
Adverse events – nausea												
From1975	randomised trials	very serious [A]	no serious inconsistency	no serious indirectness	very serious[B]	none	0/16 (0%)	2/16 (12.5%)	RR 0.2 (0.01 to 3.86)	100 fewer per 1000 (from 124 fewer to 357 more)	VERY LOW	IMPORTANT

[A] *Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.*
[B] *Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.*

Table 7: Clinical evidence profile: tinazidine versus diazepam

Quality assessment	Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tinazidine	diazepam	Relative (95% CI)	Absolute		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Patient reported outcomes												
No evidence available												
Numbers with improvement in spasticity (higher better)												
Rinne1980	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	9/15 (60%)	9/15 (60%)	RR 1 (0.56 to 1.79)	0 fewer per 1000 (from 264 fewer to 474 more)	VERY LOW	CRITICAL
AEs												
No evidence available												

[A] Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.
[B] Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.

Table 8: Clinical evidence profile: dantrolene versus diazepam

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dantrolene	diazepam	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional outcomes												
No evidence available												
Spasticity outcomes												
No evidence available												
Improvement in cramps or spasms over treatment												
Schmidt1976	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	RR: 1.19 (0.89 to 1.60)		RR: 1.19 (0.89 to 1.60)	-	MODERATE	IMPORTANT
Improvement in stiffness over treatment												
Schmidt1976	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	RR: 0.80 (0.52 to 1.24)		RR: 0.80 (0.52 to 1.24)	-	MODERATE	IMPORTANT
Improvements in gait over treatment												
Schmidt1976	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[A]	none	RR: 1.17 (0.47 to 2.89)		RR: 1.17 (0.47 to 2.89)	-	LOW	IMPORTANT

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dantrolene	diazepam	Relative (95% CI)	Absolute(95 % CI)		
Drug preference (higher better)												
Schmidt1976	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	22/42 (52.4%)	13/42 (31%)	RR 1.69 (0.99 to 2.89)	214 more per 1000 (from 3 fewer to 586 more)	MODERATE	CRITICAL
AEs												
No evidence available												

[A] *Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.*

1

2 **Table 9: Clinical evidence profile: dantrolene versus placebo**

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dantrolene	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Patient preference												
Gelenberg1973	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[B]	none	7/20 (35%)	4/20 (20%)	RR 1.75 (0.61 to 5.05)	150 more per 1000 (from 78 fewer to 810 more)	LOW	CRITICAL
Reduction in spasticity												
Tolosa1975	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	5/12 (41.7%)	3/11 (27.3%)	RR 1.53 (0.47 to 4.94)	145 more per 1000 (from 145 fewer to 1000 more)	VERY LOW	CRITICAL
Adverse events leading to treatment discontinuation												
Tolosa1975	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	2/12 (16.7%)	0/11 (0%)	Peto OR 7.45	170 more per 1000 (from 80 fewer to 410 more)	VERY LOW	CRITICAL

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dantrolene	Placebo	Relative (95% CI)	Absolute(95% CI)		
									(0.44 to 127.44)			
Adverse events - weakness												
Gelenberg1973 Tolosa1975	randomised trials	very serious [A]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/32 (65.6%)	1/31 (3.2%) 4.6%	RR 13.76 (2.84 to 66.56)	587 more per 1000 (from 85 more to 1000 more)	LOW	IMPORTANT
Adverse events - nausea												
Gelenberg1973	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/20 (35%)	0/20 (0%)	Peto OR 10.63 (2.12 to 53.21)	350 more per 1000 (from 130 more to 570 more)	HIGH	IMPORTANT
Adverse events - somnolence												
Gelenberg1973	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious [B]	none	3/20 (15%)	0/20 (0%)	Peto OR 8.23 (0.81 to 84.07)	150 more per 1000 (from 20 less to 320 more)	MODERATE	IMPORTANT

[A] Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.

[B] Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were

downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.

Table 10: Clinical evidence profile: Gabapentin versus placebo

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Existence of moderate or severe spasms at follow up (lower better)												
Cutter2000	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/21 (14.3%)	14/21 (66.7%)	RR 0.21 (0.07 to 0.64)	527 fewer per 1000 (from 240 fewer to 620 fewer)	HIGH	CRITICAL
Spasm freq >1 time per hour at follow up (lower better)												
Cutter2000	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	1/21 (4.8%)	7/21 (33.3%)	RR 0.14 (0.02 to 1.06)	287 fewer per 1000 (from 327 fewer to 20 more)	MODERATE	IMPORTANT
Spasticity worse or unchanged at follow up (lower better)												

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Cutter2000	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	6/21 (28.6%)	16/21 (76.2%)	RR 0.38 (0.18 to 0.77)	472 fewer per 1000 (from 175 fewer to 625 fewer)	MODERATE	
Modified Ashworth score >4 at follow up (lower better)												
Cutter2000	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	3/21 (14.3%)	10/21 (47.6%)	RR 0.3 (0.1 to 0.94)	333 fewer per 1000 (from 29 fewer to 429 fewer)	MODERATE	CRITICAL
Spasticity making function difficult or impossible at follow up (lower better)												
Cutter2000	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[A]	none	11/21 (52.4%)	17/21 (81%)	RR 0.65 (0.41 to 1.02)	283 fewer per 1000 (from 478 fewer to 16 more)	MODERATE	CRITICAL
AEs												
No evidence available												

[A] *Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.*

Table 11: Clinical evidence profile: Botulinum versus placebo

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Botulinum A	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Quality of life												
No evidence available												
Functional/mobility outcomes												
No evidence available												
Patient positive response - low dose (500 units)												
Hyman2000	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	serious[B]	none	13/21 (61.9%)	7/16 (43.8%)	RR 1.41 (0.74 to 2.71)	180 more per 1000 (from 114 fewer to 749 more)	VERY LOW	CRITICAL
Patient positive response - medium dose (1000 units)												
Hyman2000	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	10/21 (47.6%)	7/16 (43.8%)	RR 1.09 (0.53 to 2.22)	39 more per 1000 (from 206 fewer to 534 more)	VERY LOW	CRITICAL
Patient positive response - high dose (1500 units)												
Hyman2000	randomised trials	very serious[A]	no serious inconsistency	no serious indirectness	very serious[B]	none	8/17 (47.1%)	7/16 (43.8%)	RR 1.08 (0.51 to 2.28)	35 more per 1000 (from 214 fewer to 560 more)	VERY LOW	CRITICAL
Adverse events - weakness												

Quality assessment							Mean (sd) [n] – if parallel group data OR Mean difference (SE) [n] – if one paired value OR Proportions with event (%)		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Botulinum A	Placebo	Relative (95% CI)	Absolute(95% CI)		
Gusev2008	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[B]	none	12/55 (21.8%)	3/51 (5.9%)	RR 3.71 (1.11 to 12.39)	160 more per 1000 (from 6 more to 672 more)	MODERATE	IMPORTANT

[A] *Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.*
[B] *Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.*

Table 12: Clinical evidence profile: Intrathecal baclofen versus placebo

Quality assessment							Proportions with event (%) Mantel Haenszel test for paired categories used		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intrathecal baclofen	Placebo	Relative (95% CI)	Absolute(95% CI)		
Quality of life												
No evidence available												

Quality assessment							Proportions with event (%) Mantel Haenszel test for paired categories used		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intrathecal baclofen	Placebo	Relative (95% CI)	Absolute(95 % CI)		
Functional/mobility outcomes												
No evidence available												
Numbers with improvement in Ashworth scale (lower limb)												
Loubser 1991 Hugenholtz 1992	randomised trials	very serious risk of bias[A]	no serious inconsistency	Serious indirectness[B]	serious imprecision[C]	none	3/9 with event ONLY in baclofen gp, 6/9 with event in both gps, and 0/9 with event ONLY in placebo gp. 2/6 with event ONLY in baclofen gp, 4/6 with event in both gps, and 0/6 with event ONLY in placebo gp.		RR: 1.50 (1.05 to 2.15)	_	VERY LOW	CRITICAL
Numbers with improvement in reflex score (lower limb)												
Loubser 1991 Hugenholtz 1992	randomised trials	very serious risk of bias	no serious inconsistency	Serious indirectness[B]	serious imprecision[C]	none	2/9 with event ONLY in baclofen gp, 7/9 with event in both groups, and 0/9 with event ONLY in placebo gp. 3/6 with event ONLY in baclofen gp, 1/6 with event in both groups, and 0/6 with event ONLY in placebo gp.		RR: 1.35 (0.96 to 1.89)	_	VERY LOW	CRITICAL
Improvement in spasm score (lower limb)												
Hugenholtz 1992	randomised trials	serious risk of bias[A]	no serious inconsistency	Serious indirectness[B]	serious imprecision[C]	none	4/6 with event ONLY in baclofen gp, 2/6 with event in both groups, and 0/6 with event ONLY in placebo gp		RR: 3.0 (0.97 to 9.30)	_	VERY LOW	CRITICAL
Improvement in disability (questionnaire)												
Hugenholtz 1992	randomised trials	serious risk of bias[A]	no serious inconsistency	Serious indirectness[B]	serious imprecision[C]	none	3/6 with event ONLY in baclofen gp, 2/6 with event in both groups, and 0/6 with event ONLY in placebo gp		RR: 2.5 (0.85 to 7.32)	_	VERY LOW	CRITICAL

[A] *Outcomes were downgraded by one increment if the weighted average number of serious methodological limitations across studies was one, and downgraded by two increments if the weighted average number of serious methodological limitation across studies were two or more. Methodological limitations comprised one or more of the*

following: unclear allocation concealment, the lack of blinding, or inadequate allowance for drop-outs in the analysis. Cross-over studies were not downgraded for selection bias, as the effects of such bias would only be expected to exert effects via an order effect, and so selection bias would be less serious a limitation than in a parallel trial.

[B]Outcomes were downgraded for indirectness because the population was a mixed population, including people who did not have MS.

[C]Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if both MIDs were crossed by one or both of the 95% CIs. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.

Narrative review for outcomes not appropriate for meta-analysis

Four comparisons had outcome data that were not appropriate for meta-analysis, and so these are described narratively as follows.

Tizanidine versus placebo

Upper extremity index score (lower better)

One study[118]assessed the effects of tizanidine and placebo on arm function, as measured by the upper extremity function score. It reported its results using parametric statistics, although this was inappropriate given the ordinal nature of this measure. Its data suggested no clear effect [Tizanidine 0.48 (0.74), placebo 0.52(0.77)] although the validity of this finding is suspect in view of the inappropriate analysis.

Botulinum versus placebo

Improvement in muscle tone

No data were presented, but it was stated that: "At week 8 the difference in the proportion of patients who had an improvement of ≥ 1 point on the MAS for leg adductor muscle tone approached significance (p=0.067)".

Intrathecal baclofen versus placebo

One study[143] evaluated the effects of intrathecal baclofen and intrathecal saline placebo on spasm, spasticity, pain and two measures of quality of life: sickness impact profile (SIP) and Hopkins Symptom Check List (HSCL). As the groups differed at baseline for spasm, spasticity and pain, a non-parametric Cohen estimate of between-group effect sizes was carried out (Table 13).

Table 13: Clinical evidence profile: intrathecal baclofen versus placebo

	Baclofen (n=10) mean(sd)	Placebo (n=12) mean(sd)	Cohen effect sizes, estimating the group difference in the magnitude of the change between baseline and 3 months	U Wilcoxon p value
spasm at 3 months (lower better)	1.65(1.1)	1.81(0.76)	0.2 (weakly favours baclofen)	<0.05
Ashworth scale at 3 months (lower better)	1.51(1.2)	2.87(0.57)	1.40 (strongly favours baclofen)	<0.01
Self-reported pain score at 3 months (lower better)	2.75(3.22)	5.94(3.57)	0.94 (strongly favours baclofen)	<0.05
Overall SIP at 3 months (lower better)	27.79(5.32)	28.98(8.83)	No effect size given	NS
Overall HSCL at 3 months (lower better)	20.67(11.78)	28.22(18.43)	No effect size given	NS

One study[141,142] demonstrated that intrathecal baclofen led to significantly ($p<0.01$ for all) greater improvements than placebo in both upper and lower limb Ashworth scale, spasm scale and reflex scale 6 hours after a bolus injection. No data were provided for the placebo group, so only the direction of effect is possible to report.

In a similar study on a different neurological disease population [141] intrathecal baclofen led to significantly ($p<0.01$ for all) greater improvements than placebo in both upper and lower limb Ashworth scale, spasm scale and reflex scale 6 hours after a bolus injection. No data were provided for the placebo group, so only the direction of effect is possible to report.

One study[174] showed that a group of spinal cord injured patients all improved with a bolus injection of intrathecal baclofen but that no improvements were seen in the placebo group. Improvement was denoted by a reduction in the mean Ashworth score or the mean spasm score of 2 or more points for at least 4 hours.

One cross-over study[100]assessed the effects of intrathecal baclofen and placebo on the proportion of people with improvements upper limb Ashworth scale, spasm and reflexes. It was not possible to calculate Mantel-Haenszel risk ratios for paired categorical outcomes as there were insufficient people with the event.

For the Ashworth scale, one patient showed an improvement in both treatments, but no patients showed an improvement in just one of the treatments. This indicates no difference in effect, though the uncertainty of this effect is unknown. For spasm score, no patients showed an improvement in both or just one of the treatments. This also indicates no difference in effect, though the uncertainty of this effect is unknown. For reflex score, no patients showed an improvement in both treatments, but one patient showed an improvement in just the baclofen treatment. This indicates a slight effect in favour of intrathecal baclofen, though the uncertainty of this effect is unknown.

1.1.6 Summary of included economic evidence

None

1.1.7 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.8 Unit costs

Table 14: Unit costs

Drug (preparation)	Dosage (a)	Cost per day (a)	Cost per year (a)
Baclofen (10mg tablets)	60-100mg daily (b)	£0.13 to £0.22	£47.19 to £78.65
Baclofen (intrathecal infusion), test dose	25–50 micrograms (c)	£2.50	Not applicable
Baclofen (intrathecal infusion, 2mg/1ml – 5ml ampoules), maintenance	Maximum 2 mg daily (c)	£50/£10 (single use ampoule/ampoules used for multiple treatments)	£18,250/£3,650(single use ampoule/ampoules used for multiple treatments)
Tizanidine (2mg / 4mg tablets)	2-36 mg daily (d)	£0.09 to £3.04	£31.30 to £1,108.69
Gabapentin (300mg capsule)	Up to 900mg TID (e)	£0.29	£107.42
Dantrolene sodium (25mg capsule)	75 mg TID (f)	£1.52	£554.18
Diazepam (10mg tablets)	60mg daily (g)	£0.23	£82.91
Botulinum toxin Type A (powder for solution for injection vials)	500-1500 units of Dysport (g)	£92.40-£462	£369.60-£1,848

Acronyms: TID= three times a day.

(a) Dosing and cost source: Drug tariff, BNF[2], Accessed 10/11/21

(b) 60mg daily maintenance dose, 100mg maximum dose

(c) Test dose 25–50 micrograms, to be given over at least 1 minute via catheter or lumbar puncture, then increased in steps of 25 micrograms (max. per dose 100 micrograms), not given more often than every 24 hours to determine appropriate dose, then dose-titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1.4 mg daily for spasticity of cerebral origin) retaining some spasticity to avoid sensation of paralysis. Only 1 ml of 5ml ampoule required a day. Presented cost assuming the cost of full 5ml ampoule as rest cannot be used and the cost if vial can be used for other treatments.

(d) Initially 2 mg daily, then increased in steps of 2 mg daily in divided doses, increased at intervals of at least 3–4 days and adjust according to response; usual dose up to 24 mg daily in 3–4 divided doses; maximum 36 mg per day.

(e) Initially 300 mg once daily for 1–2 weeks, then 300 mg twice daily for 1–2 weeks, then 300 mg 3 times a day for 1–2 weeks, alternatively initially 100 mg 3 times a day, then increased in steps of 100 mg 3 times a day, every 1–2 weeks, adjusted according to response: usual maximum 900 mg 3 times a day

(f) Initially 25 mg daily, then increased to up to 100 mg 4 times a day, dose increased at weekly intervals: usual dose 75 mg 3 times a day.

(g) For muscle spasm of varied aetiology: For Adult: 2–15 mg daily in divided doses, then increased if necessary to 60 mg daily, adjusted according to response, dose only increased in spastic conditions.

(a) Hyman (2000): Dysport 500 - 1500 Units every 3 months, equivalent to 150-500 units of Xeomin (conversion from Scaglione (2016).[25] Different botulinum toxin type A products have different potency and the units are not equivalent. Clinical conversion ratios: Botox:Dysport 1:3 and Botox:Xeomin 1:1. Therefore, a dose of 300 units of Dysport is equivalent to 100 units of Botox/Xeomin.

1.1.9 Evidence statements

Effectiveness

For evidence that could be assessed using GRADE, see summary of evidence in Tables 3-12.

Economic

- No relevant economic evaluations were identified.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The committee agreed that all outcomes included in the protocol were of critical importance for decision-making. The outcomes included spasticity scale, patient-reported measures to assess spasticity, Health-related Quality of Life (HRQoL), Visual Analogue Scales to assess pain, improvement in sleep, comfort and posture positioning, functional scales to quantify the level of spasticity and impact on patients and carers. The most commonly used outcomes were those evaluating changes in spasticity, such as the Ashworth scale or patient-reported spasticity outcomes which ranged from global satisfaction to rating scales for spasms and stiffness. The Ashworth and modified Ashworth scale for spasticity, however, are known to have serious limitations. Functional improvements were also regarded as important sensitive indicators of improvement, as even small changes in spasticity can have a major impact on functioning.

No new evidence meeting the evidence review protocol was identified since the last update of the guideline.

1.1.10.2 The quality of the evidence

The quality of the evidence from was generally low or very low, with the main methodological limitations being a lack of allocation concealment, insufficient blinding and inadequate handling of drop-outs in the analyses. Many trials had limited numbers of participants, leading to possible type II errors. A network meta-analysis was not possible due to the differing populations and the lack of common outcomes across studies.

1.1.10.3 Benefits and harms

The committee highlighted that it was important to emphasise that the management of spasticity in MS should be tailored to the needs of the individual patient and their specific treatment goals given how differently spasticity can affect different people at different stages in the course of their disease. Therefore, recommendations were made around assessing for and treating the precipitating and prolonging factors to symptomatic spasticity. As some people with MS may use their spasticity to support them in maintaining posture when transferring or standing, the treatment of spasticity has the potential to cause greater levels of disability and it was, therefore, felt to be worth re-iterating the need to consider the less obvious immediate risks of treating spasticity.

Gabapentin had the clearest clinical benefits, followed by baclofen, tizanidine and dantrolene. Baclofen was recommended at the first line option due to the possibility of dependence and withdrawal problems associated with gabapentin. The committee confirmed that gabapentin is often used in current clinical practice and that the potential benefits outweigh the prescribing issues associated with its use. The committee highlighted that there are side effects of these intervention such as muscle weakness and these need to be discussed with the person when considered offering baclofen or gabapentin. The combination of baclofen and gabapentin is offered when neither agent by itself manages to control symptoms.

Although there have been no new pieces of evidence since the previous guideline, they have been amended to clarify the importance of gradually increasing doses of medication to the dosage at which an individual will respond. Some people with multiple sclerosis make functional use of their increased muscle tone from spasticity, for example to help them walk. For these people reduction in spasticity could lead to more difficulty with certain motor

function and this should be discussed with the person. The role of therapists in patient assessment and treatment has also been made more explicit.

Where a patient's treatment goals are not being met by first- and second-line pharmacological therapies and appropriate physical assessments and precipitating or prolonging factors have been addressed, there is a need to consider other treatment approaches which may be delivered by a service dedicated to the more specialist management of spasticity such as rehabilitation medicine. The committee removed the recommendations on third- and fourth-line options due to the lack of clinical and health economic evidence. These treatments should only be considered by specialists.

Due to the limited evidence the committee made a research recommendation for future studies to be conducted on all of the interventions stated in the review protocol.

There is NICE guidance of the use of cannabis-derived medication for the treatment of spasticity in MS which has been published since the MS guideline was last revised. The specific guideline on cannabis-derived medication is referenced and as current practice is for this to be considered for prescription by services that specialise in the management of spasticity as part of a holistic approach to assessment and treatment.

The committee noted that the BNF states that both gabapentin and baclofen can have central nervous system (CNS) depressant effects, which might affect the ability to perform skilled tasks. There is also a potential increased risk of respiratory depression (as advised by the MHRA) when using gabapentin in combination with other CNS depressants and people with neurological disease (such as MS) may be at higher risk of this.

1.1.10.4 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review. Unit costs were presented to aid committee consideration of cost-effectiveness. The annual cost of the drugs varied depending on the prescribed dose and was between £47–£79 for oral baclofen, £108 for gabapentin, £31–£1,109 for tizanidine, £554 for dantrolene, and £82 for diazepam. The committee noted that there may be additional costs associated with prescribing gabapentin as it has been reclassified as a Class C controlled substance. For example, additional healthcare professionals time may be needed for evaluating people for a history of drug abuse before prescribing gabapentin, and for monitoring for signs of abuse and dependence. Furthermore, it was highlighted to the committee that the actual cost of intrathecal baclofen includes the cost of administering the drug as well as the drug costs (which are between £3,650 and £18,250, depending on whether an ampoule can be used for multiple treatments). The administration costs although not presented to the committee are considered to be significant. The unit cost of botulinum toxin A was also presented and was between £370 and £1,848 for 4 treatments a year depending on the dose.

No new clinical evidence was identified since the previous MS guideline update. The evidence in the last update suggested that gabapentin is more effective than oral baclofen. Gabapentin remains more expensive than oral baclofen. Considering the re-classification of gabapentin as a Class C controlled substance and the MHRA warning around respiratory depression, the committee agreed to change the recommendation to recommend oral baclofen as the first line drug treatment for spasticity, with gabapentin to be considered as an alternative if oral baclofen is not tolerated. The committee noted that in current practice oral baclofen is already the more commonly prescribed drug for spasticity and this change in recommendation will not lead to a change in practice.

Based on committee consensus, the committee also altered the recommendations to clarify the importance of gradually increasing doses of medication to the dosage at which an individual will respond. This change is not expected to have a significant resource impact.

Due to a lack of clinical and cost effectiveness evidence for other pharmacological treatments for spasticity the committee removed the previous recommendations on third- and fourth-line treatments. These treatments should only be considered by specialists. Referring people to specialist spasticity services earlier in the pathway was also not anticipated to have a significant resource impact as this already occurs in current practice, with only a small proportion of the MS population requiring such services. Furthermore, the committee highlighted that early interventions are in general associated with better clinical outcomes, so this small proportion of patients may do better in the long term and need less input from the local services.

Overall, the changes to the recommendations are not expected to result in significantly greater resources being required to support the assessment and treatment of spasticity in people with MS. It may be that there are resource savings realised through a reduction in the downstream complications of inappropriately or untreated spasticity.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.21 to 1.5.29 and the research recommendation on spasticity.

1.1.12 References

1. Bensmail D, Ward AB, Wissel J, Motta F, Saltuari L, Lissens J et al. Cost-effectiveness modeling of intrathecal baclofen therapy versus other interventions for disabling spasticity. Neurorehabilitation and Neural Repair. 2009; 23(6):546-552

2. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 2021. Available from: https://bnf.nice.org.uk/ Last accessed: 06 October 2021.

3. Brar SP, Smith MB, Nelson LM, Franklin GM, Cobble ND. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. Archives of Physical Medicine and Rehabilitation. 1991; 72(3):186-189

4. Cutter NC, Scott DD, Johnson JC, Whiteneck G. Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. Archives of Physical Medicine and Rehabilitation. 2000; 81(2):164-169

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

6. From A, Heltberg A. A double-blind trial with baclofen (Lioresal) and diazepam in spasticity due to multiple sclerosis. Acta Neurologica Scandinavica. 1975; 51(2):158-166

7. Gelenberg AJ, Poskanzer DC. The effect of dantrolene sodium on spasticity in multiple sclerosis. Neurology. 1973; 23(12):1313-1315

8. Gusev YI, Banach M, Simonow A, Skoromets A, Czlonkowska A, Shmidt T et al. Efficacy and safety of botulinum type a toxin in adductor spasticity due to multiple sclerosis. Journal of Musculoskeletal Pain. 2008; 16(3):175-188

9. Hoogstraten MC, Van Der Ploeg RJO, Burg W, Vreeling A, Van MS, Minderhoud JM. Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. Acta Neurologica Scandinavica. 1988; 77(3):224-230

10. Hugenholtz H, Nelson RF, Dehoux E, Bickerton R. Intrathecal baclofen for intractable spinal spasticity--a double-blind cross-over comparison with placebo in 6 patients. Canadian Journal of Neurological Sciences. 1992; 19(2):188-195

11. Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B et al. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. Journal of neurology, neurosurgery, and psychiatry. 2000; 68(6):707-712

12. Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy K et al. Botulinum toxin (Dysport) treatment of upper leg adductor spasticity in multiple sclerosis: a prospective, randomised, double-blind, placebo controlled, dose ranging study. European Journal of Neurology. 1997; 4 Suppl 1:S82

13. Lapierre Y, Bouchard S, Tansey C, Gendron D, Barkas WJ, Francis GS. Treatment of spasticity with tizanidine in multiple sclerosis. Canadian Journal of Neurological Sciences. 1987; 14(3 Suppl):513-517

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

15. Meythaler JM, DeVivo MJ, Hadley M. Prospective study on the use of bolus intrathecal baclofen for spastic hypertonia due to acquired brain injury. Archives of Physical Medicine and Rehabilitation. 1996; 77(5):461-466

16. Meythaler JM, Guin-Renfroe S, Brunner RC, Hadley MN. Intrathecal baclofen for spastic hypertonia from stroke. Stroke. 2001; 32(9):2099-2109

17. Middel B, Kuipers-Upmeijer H, Bouma J, Staal M, Oenema D, Postma T et al. Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. Journal of neurology, neurosurgery, and psychiatry. 1997; 63(2):204-209

18. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

19. Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. Journal of Neurosurgery. 1996; 85(3):452-457

20. Orsnes GB, Sørensen PS, Larsen TK, Ravnborg M. Effect of baclofen on gait in spastic MS patients. Acta Neurologica Scandinavica. 2000; 101(4):244-248

21. Rinne U. Tizanidine treatment of spasticity in multiple sclerosis and chronic myelopathy. Current Therapeutic Research. 1980; 28:827-836

22. Roussan M, Terrence C, Fromm G. Baclofen versus diazepam for the treatment of spasticity and long-term follow-up of baclofen therapy. Pharmatherapeutica. 1985; 4(5):278-284

23. Sachais BA, Logue JN, Carey MS. Baclofen, a new antispastic drug. A controlled, multicenter trial in patients with multiple sclerosis. Archives of Neurology. 1977; 34(7):422-428

24. Sawa GM, Paty DW. The use of baclofen in treatment of spasticity in multiple sclerosis. Canadian Journal of Neurological Sciences. 1979; 6(3):351-354

25. Scaglione F. Conversion ratio between botox, dysport, and xeomin in clinical practice. Toxins. 2016; 8(3):65

26. Schmidt RT, Lee RH, Spehlmann R. Comparison of dantrolene sodium and diazepam in the treatment of spasticity. Journal of neurology, neurosurgery, and psychiatry. 1976; 39(4):350-356

27. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev. 2003; (4):CD001332

28. Smith C, Birnbaum G, Carter JL, Greenstein J, Lublin FD. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. US Tizanidine Study Group. Neurology. 1994; 44(11 Suppl 9):S34-S42

29. Smolenski C, Muff S, Smolenski-Kautz S. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Current Medical Research and Opinion. 1981; 7(6):374-383

30. Stien R, Nordal HJ, Oftedal SI, Slettebo M. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. Acta Neurologica Scandinavica. 1987; 75(3):190-194

31. Tolosa ES, Soll RW, Loewenson RB. Letter: Treatment of spasticity in multiple sclerosis with dantrolene. JAMA. 1975; 233(10):1046

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

Appendices

Appendix A – Review protocols

Review protocol for pharmacological management of spasticity

ID	Field	Content
0.	PROSPERO registration number	CRD42021229540
1.	Review title	Pharmacological management of spasticity
2.	Review question	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of pharmacological interventions for spasticity?
3.	Objective	To determine to the most clinically effective pharmacological treatment for spasticity in people with MS.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Date limitations: databased will be searched from 2014 onwards (last search conducted for CG186) • English language studies

		• Human studies • Validated study filters for systematic reviews and RCTs The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Multiple sclerosis
6.	Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people (≤18 years).
7.	Intervention	• Baclofen (oral) (Lioresal)- used more widely • Baclofen (intrathecal) – to be kept separate to oral • Tizanidine (Zanaflex) • Gabapentin (Neurontin) • Dantrolene sodium (Dantrium) • Benzodiazepines (Diazepam, clonazepam) • Botulinum toxin (Azzalure, Bocouture, Botox, Dysport, Vistabel, Xeomin) • Pregabalin (Lyrica) • Phenol- used by injection in 2 way: intrathecal and peripheral nerve block (consider 2 separate interventions) • Combinations of the above (Report if any non-pharmacological interventions used alongside these drugs)

8.	Comparator/	Interventions will be compared to each other (both within and between classes), to placebo/sham, or to usual care or no treatment.
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion if they have an appropriate washout period which is no less than a week. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. We consider RCT data to be the best evidence for reviews of interventions. In addition, the surveillance review and GC have highlighted the existence of relevant RCTs in this area. Therefore, if no RCT data is available observational data will not be considered due to the risk of confounding variables influencing the study results, reducing our confidence in the overall results of the review. Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	This review will inform the update of the recommendations 1.5.16-1.5.24 in CG 186.

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical.
		• Spasticity scales for example:
		  ○ Modified Ashworth scale
		  ○ Tardieu Scale
		  ○ Muscle Elastography MS Scale (MEMSs)
		  ○ Fugl Meyer Scale (FMS)
		• Patient reported measures of spasticity for example:

		○ Penn Spasm Frequency Scale ○ Numeric Rating Scale for Spasticity (NRS-S) ○ MS Spasticity Scale-88 (MSSS) ○ Patient-reported Impact of Spasticity Measure (PRISM) • Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale • Adverse effects of treatment for example: ○ Any adverse events ○ Adverse events leading to withdrawal ○ Drowsiness ○ Weakness ○ Nausea ○ Mobility • Pain scales for example visual analogue scale (VAS) • Improvement in sleep • Comfort and posture positioning (self-reported) • Functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), the Functional Assessment of Multiple Sclerosis (FAMS), the National Fatigue Index (NFI) or the MS walking scale. • Impact on patients/ carers **Follow up:** • 3-6 months (minimum of 3 months but can include 1-3 months and downgrade) • >6 months – 1 year (data from >1 year follow up may be included but will be downgraded)

13.	Secondary outcomes (important outcomes)	n/a see comments above
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where

		possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. To maximise the amount of data for meta-analysis, where multiple scales have been used for an outcome such as mobility, fatigue or spasticity, the most commonly reported ones across studies will be extracted and meta-analysed with priority given to those included in CG 186. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 186. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available, meta-regression or NMA-meta-regression will be conducted. WinBUGS will be used for network meta-analysis, if possible, given the data identified.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) • According to disability (EDSS <6 and EDSS ≥6) • Disease modifying treatment status (currently using and not currently using) • Drug doses (standard doses vs non-standard doses which will be discussed and agreed with the GC prior to presenting the evidence to them) • Routes of administration particularly baclofen (intrathecal vs oral) • People receiving palliative care

18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	October 2020	
22.	Anticipated completion date	July 2022	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐

24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail MultipleSclerosisUpdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Dr Sharon Swain [Guideline lead] Dr Saoussen Ftouh [Senior systematic reviewer] Nicole Downes [Systematic reviewer] Sophia Kemmis Betty [Senior health economist] Lina Gulhane [Information specialist] Emma Clegg [Information specialist] Kate Ashmore [Project Manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part

		of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Multiple sclerosis, spasticity, pharmacological management, Baclofen, Tizanidine, Gabapentin, Dantrolene sodium, Benzodiazepines, Botulinum toxin Botox, Pregabalin, Phenol	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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1 Review protocol for health economic literature review

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[18] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B – Literature search strategies

This literature search strategy was used for the following review:

- The clinical and cost effectiveness of pharmacological interventions for spasticity for adults with MS, including people receiving palliative care.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[18]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 15: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2014 – 08 September 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, children)
Embase (OVID)	01 January 2014 – 08 September 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, conference abstracts, children)
The Cochrane Library (Wiley)	Cochrane Reviews 2014 to 2021 Issue 9 of 12 CENTRAL 2014 to 2021 Issue 9 of 12	None Exclusions (conference abstracts & clinical trials)
Epistemonikos (The Epistemonikos Foundation)	01 January 2014 – 08 September 2021	Systematic Reviews Exclusions (Cochrane Reviews)

Medline (Ovid) search terms

1.	exp Paraparesis/
2.	parapares*.ti,ab.
3.	Muscle Spasticity/
4.	(spastic* or spasm*).ti,ab.
5.	exp Spasm/
6.	Mobility limitation/ or Movement/ or Locomotion/

7.	((limit* or difficult* or disorder* or impair*) adj2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)).ti,ab.
8.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tens*) adj2 (muscle* or muscular)).ti,ab.
9.	or/1-8
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	exp Animals, Laboratory/
23.	exp Animal Experimentation/
24.	exp Models, Animal/
25.	exp Rodentia/
26.	(rat or rats or rodent* or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
30.	28 not 29
31.	limit 30 to English language
32.	baclofen/
33.	(Baclofen* or baclophen* or ciba-34,647-ba or (chlorophenyl adj gaba) or lioresal).ti,ab.
34.	gabapentin/
35.	(gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab.
36.	pregabalin/
37.	(pregabalin* or 3 isobutyl gaba or 3-aminomethyl-5-methylhexanoic acid or lyrica).ti,ab.
38.	dantrolene/
39.	(Dantrolene or Dantrium).ti,ab.
40.	benzodiazepines/ or clonazepam/ or exp diazepam/
41.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*).ti,ab.
42.	exp Imidazolines/
43.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex).ti,ab.
44.	exp Botulinum Toxins/
45.	botulin*.ti,ab.
46.	(botulin* or onabotulinumtoxin* or abobotulinumtoxin* or incobotulinumtoxin* or prabotulinumtoxin* or rimabotulinum*).ti,ab.
47.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau).ti,ab.

48.	Phenol/
49.	(phenol adj3 (inject* or intrathecal* or pump* or liquid*)).ti,ab.
50.	or/32-49
51.	31 and 50
52.	randomized controlled trial.pt.
53.	controlled clinical trial.pt.
54.	randomi#ed.ti,ab.
55.	placebo.ab.
56.	randomly.ti,ab.
57.	Clinical Trials as topic.sh.
58.	trial.ti.
59.	or/52-58
60.	Meta-Analysis/
61.	exp Meta-Analysis as Topic/
62.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
63.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
64.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
65.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
66.	(search* adj4 literature).ab.
67.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
68.	cochrane.jw.
69.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
70.	or/60-69
71.	51 and (59 or 70)
72.	Epidemiologic studies/
73.	Observational study/
74.	exp Cohort studies/
75.	(cohort adj (study or studies or analys* or data)).ti,ab.
76.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
77.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
78.	Controlled Before-After Studies/
79.	Historically Controlled Study/
80.	Interrupted Time Series Analysis/
81.	(before adj2 after adj2 (study or studies or data)).ti,ab.
82.	exp case control study/
83.	case control*.ti,ab.
84.	Cross-sectional studies/
85.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	or/72-85
87.	51 and 86
88.	71 or 87

1 **Embase (Ovid) search terms**

1.	exp paraplegia/
2.	parapares*.ti,ab.
3.	spastic paraplegia/
4.	spastic paresis/
5.	spasticity/
6.	(spastic* or spasm*).ti,ab.
7.	exp muscle spasm/
8.	walking difficulty/
9.	body movement/ or limb movement/ or locomotion/ or voluntary movement/
10.	((limit* or difficult* or disorder* or impair*) adj2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)).ti,ab.
11.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tens*) adj2 (muscle* or muscular)).ti,ab.
12.	or/1-11
13.	letter.pt. or letter/
14.	note.pt.
15.	editorial.pt.
16.	(conference abstract or conference paper).pt.
17.	case report/ or case study/
18.	(letter or comment*).ti.
19.	or/13-17
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental Animal/
26.	animal model/
27.	exp Rodent/
28.	(rat or rats or rodent* or mouse or mice).ti.
29.	or/21-28
30.	12 not 29
31.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
32.	30 not 31
33.	limit 32 to English language
34.	baclofen/
35.	(Baclofen* or baclophen* or ciba-34,647-ba or (chlorophenyl adj gaba) or lioresal).ti,ab.
36.	gabapentin/
37.	(gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab.
38.	pregabalin/
39.	(pregabalin* or 3 isobutyl gaba or 3-aminomethyl-5-methylhexanoic acid or lyrica).ti,ab.
40.	dantrolene/
41.	(Dantrolene or Dantrium).ti,ab.
42.	benzodiazepine/ or benzodiazepine derivative/
43.	clonazepam/

44.	diazepam/
45.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*).ti,ab.
46.	imidazoline/ or imidazole derivative/
47.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex).ti,ab.
48.	botulinum toxin/
49.	botulin*.ti,ab.
50.	(botulin* or onabotulinumtoxin* or abobotulinumtoxin* or incobotulinumtoxin* or prabotulinumtoxin* or rimabotulinum*).ti,ab.
51.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau).ti,ab.
52.	phenol/
53.	(phenol adj3 (inject* or intrathecal* or pump* or liquid*)).ti,ab.
54.	or/34-53
55.	33 and 54
56.	random*.ti,ab.
57.	factorial*.ti,ab.
58.	(crossover* or cross over*).ti,ab.
59.	((doubl* or singl*) adj blind*).ti,ab.
60.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
61.	crossover procedure/
62.	single blind procedure/
63.	randomized controlled trial/
64.	double blind procedure/
65.	or/56-64
66.	systematic review/
67.	meta-analysis/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	55 and (65 or 76)
78.	Clinical study/
79.	Observational study/
80.	Family study/
81.	Longitudinal study/
82.	Retrospective study/
83.	Prospective study/
84.	Cohort analysis/

85.	Follow-up/
86.	cohort*.ti,ab.
87.	85 and 86
88.	(cohort adj (study or studies or analys* or data)).ti,ab.
89.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
90.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
91.	(before adj2 after adj2 (study or studies or data)).ti,ab.
92.	exp case control study/
93.	case control*.ti,ab.
94.	cross-sectional study/
95.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
96.	or/78-84,87-95
97.	55 and 96
98.	77 or 97

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Paraparesis] explode all trees
#2.	parapares*:ti,ab
#3.	MeSH descriptor: [Muscle Spasticity] this term only
#4.	(spastic* or spasm*):ti,ab
#5.	MeSH descriptor: [Spasm] explode all trees
#6.	MeSH descriptor: [Mobility Limitation] this term only
#7.	MeSH descriptor: [Movement] this term only
#8.	MeSH descriptor: [Locomotion] this term only
#9.	((limit* or difficult* or disorder* or impair*) NEAR/2 (walk* or ambulat* or mobility or move or moving or movement or locomotion or muscle* or muscular)):ti,ab
#10.	((stiff* or heaviness or heavy or contract* or tone or weak* or tight* or tens*) NEAR/2 (muscle* or muscular)):ti,ab
#11.	(OR #1-#10)
#12.	MeSH descriptor: [Baclofen] this term only
#13.	(Baclofen* or baclophen* or lioresal):ti,ab
#14.	(chlorophenyl NEAR gaba):ti,ab
#15.	MeSH descriptor: [Gabapentin] this term only
#16.	(gabapentin* or 1aminomethylcyclohexaneacetic acid or convalis or Neurontin):ti,ab
#17.	MeSH descriptor: [Pregabalin] this term only
#18.	(pregabalin* or 3 isobutyl gaba or 3aminomethyl5methylhexanoic acid or lyrica):ti,ab
#19.	MeSH descriptor: [Dantrolene] this term only
#20.	(Dantrolene or Dantrium):ti,ab
#21.	MeSH descriptor: [Benzodiazepines] this term only
#22.	MeSH descriptor: [Clonazepam] this term only
#23.	MeSH descriptor: [Diazepam] explode all trees
#24.	(benzodiazepinone* or clonazaepam* or diazepam* or Nordazepam*):ti,ab
#25.	MeSH descriptor: [Imidazolines] explode all trees
#26.	(imidazoline* or clonidine* or catapres* or clo*elin* or dixarit or Tizanidine* or Zanaflex):ti,ab

#27.	MeSH descriptor: [Botulinum Toxins] explode all trees
#28.	botulin*:ti,ab
#29.	(botulin* or onabotulinumtoxin* or abobotulinumtoxin* or incobotulinumtoxin* or prabotulinumtoxin* or rimabotulinum*):ti,ab
#30.	(Azzalure or Bocouture or Botox or Dysport or Vistabel or Xeomin or Myobloc or Jeuveau):ti,ab
#31.	MeSH descriptor: [Phenols] explode all trees
#32.	(phenol NEAR/3 (inject* or intrathecal* or pump* or liquid*)):ti,ab
#33.	(OR #12-#32)
#34.	#11 AND #33
#35.	conference:pt or (clinicaltrials or trialsearch):so
#36.	#34 NOT #35

Epistemonikos search terms

1.	((advanced_title_en:(spasticity) OR advanced_abstract_en:(spasticity)) OR (advanced_title_en:(Paraparesis) OR advanced_abstract_en:(Paraparesis)) OR (advanced_title_en:(spasm) OR advanced_abstract_en:(spasm)) AND (advanced_title_en:(baclofen) OR advanced_abstract_en:(baclofen)) OR (advanced_title_en:(gabapentin) OR advanced_abstract_en:(gabapentin)) OR (advanced_title_en:(pregabalin) OR advanced_abstract_en:(pregabalin)) OR (advanced_title_en:(dantrolene) OR advanced_abstract_en:(dantrolene)) OR (advanced_title_en:(benzodiazepine) OR advanced_abstract_en:(benzodiazepine)) OR (advanced_title_en:(imidazoline) OR advanced_abstract_en:(imidazoline)) OR (advanced_title_en:(botulinum) OR advanced_abstract_en:(botulinum)) OR (advanced_title_en:(phenol) OR advanced_abstract_en:(phenol))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search with the Multiple Sclerosis population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics. Searches for quality of life studies were run for general information.

Table 16: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, children)
Embase	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, conference abstracts, children)
Centre for Research and Dissemination (CRD)	HTA – 01 January 2014 – 31 March 2018 NHSEED – 01 January 2014 – March 2015	None

Database	Dates searched	Search filter used
The International Network of Agencies for Health Technology Assessment (INAHTA)	01 January 2018 – 07 September 2021	None

1 **Medline (Ovid) search terms**

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	*Demyelinating Diseases/
9.	*Demyelinating Autoimmune Diseases, CNS/
10.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
11.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
12.	Venous Insufficiency/cf, co, di, dg, et [Cerebrospinal Fluid, Complications, Diagnosis, Diagnostic Imaging, Etiology]
13.	(Devic* adj (disease or syndrome)).ti,ab.
14.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
15.	exp Optic Neuritis/
16.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
17.	(NMO or NMOSD).ti,ab.
18.	or/1-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or rodent* or mouse or mice).ti.

36.	or/29-35
37.	18 not 36
38.	limit 37 to English language
39.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
40.	38 not 39
41.	Economics/
42.	Value of life/
43.	exp "Costs and Cost Analysis"/
44.	exp Economics, Hospital/
45.	exp Economics, Medical/
46.	Economics, Nursing/
47.	Economics, Pharmaceutical/
48.	exp "Fees and Charges"/
49.	exp Budgets/
50.	budget*.ti,ab.
51.	cost*.ti.
52.	(economic* or pharmaco?economic*).ti.
53.	(price* or pricing*).ti,ab.
54.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
55.	(financ* or fee or fees).ti,ab.
56.	(value adj2 (money or monetary)).ti,ab.
57.	or/41-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.

75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	40 and 57
79.	40 and 77
80.	78 or 79

1 **Embase (Ovid) search terms**

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	demyelinating disease/
9.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
10.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
11.	vein insufficiency/co, di, et [Complication, Diagnosis, Etiology]
12.	(Devic* adj (disease or syndrome)).ti,ab.
13.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
14.	exp optic neuritis/
15.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
16.	(NMO or NMOSD).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	(conference abstract or conference paper).pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/18-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or rodent* or mouse or mice).ti.
34.	or/26-33
35.	17 not 34

36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	limit 37 to English language
39.	health economics/
40.	exp economic evaluation/
41.	exp health care cost/
42.	exp fee/
43.	budget/
44.	funding/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/39-51
53.	quality adjusted life year/
54.	"quality of life index"/
55.	short form 12/ or short form 20/ or short form 36/ or short form 8/
56.	sickness impact profile/
57.	(quality adj2 (wellbeing or well being)).ti,ab.
58.	sickness impact profile.ti,ab.
59.	disability adjusted life.ti,ab.
60.	(qal* or qtime* or qwb* or daly*).ti,ab.
61.	(euroqol* or eq5d* or eq 5*).ti,ab.
62.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
63.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
64.	(hui or hui1 or hui2 or hui3).ti,ab.
65.	(health* year* equivalent* or hye or hyes).ti,ab.
66.	discrete choice*.ti,ab.
67.	rosser.ti,ab.
68.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
69.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
70.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
71.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
72.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
73.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
74.	or/53-73
75.	38 and 52
76.	38 and 74
77.	75 or 76

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Multiple Sclerosis EXPLODE ALL TREES

#2.	(((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	(MS)
#5.	MeSH DESCRIPTOR Myelitis, Transverse EXPLODE ALL TREES
#6.	(transverse myelitis)
#7.	MeSH DESCRIPTOR Demyelinating Diseases EXPLODE ALL TREES
#8.	((Demyelinat* adj2 (syndrome or disease)))
#9.	(Chronic Cerebrospinal Venous Insufficiency)
#10.	MeSH DESCRIPTOR Venous Insufficiency
#11.	(((Devic or "devic's") adj (disease or syndrome)))
#12.	(((clinically isolated or radiologically isolated) adj syndrome))
#13.	MeSH DESCRIPTOR Optic Neuritis EXPLODE ALL TREES
#14.	(Neuromyelitis Optica)
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

1 **INAHTA search terms**

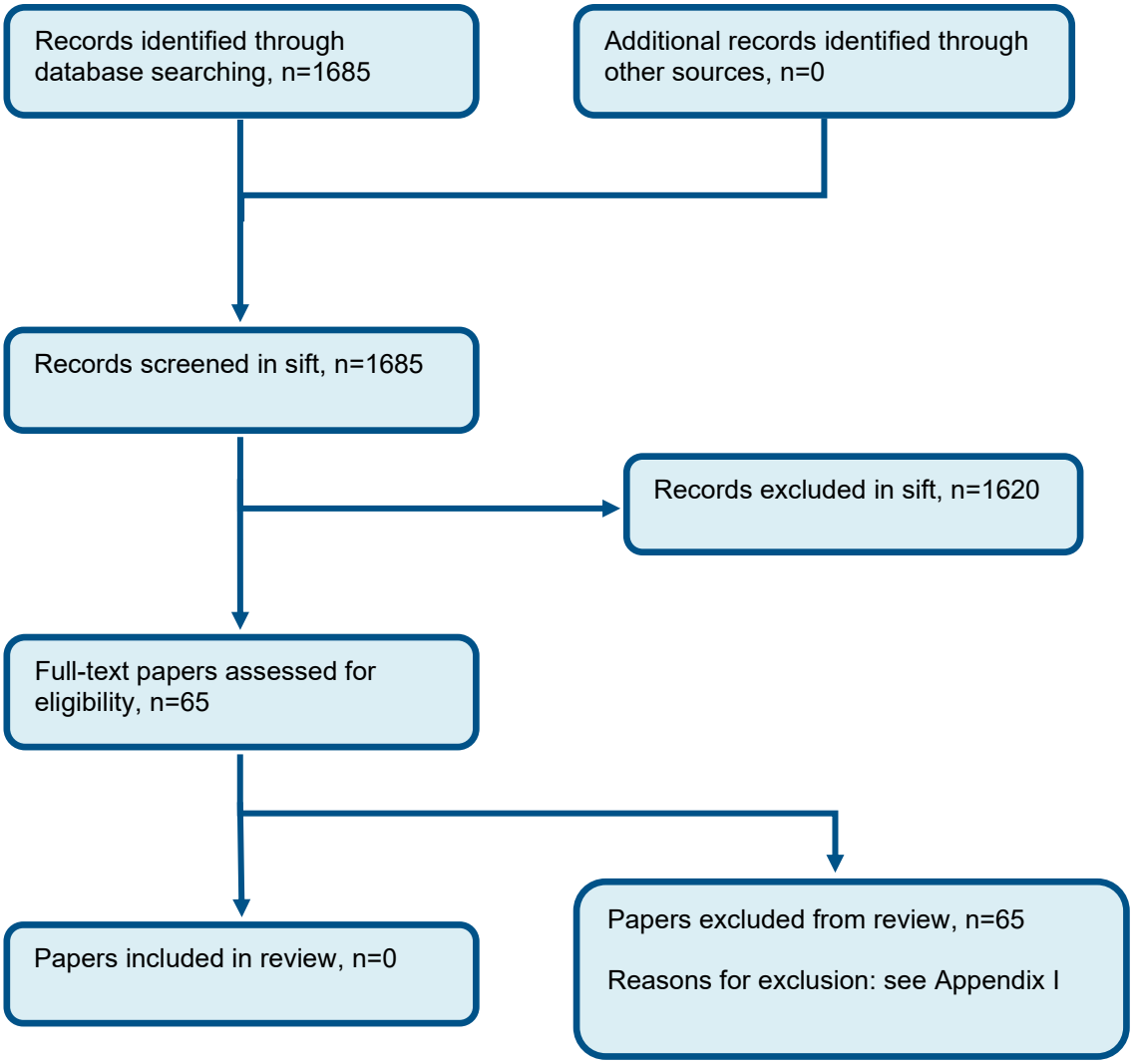
1.	(multiple sclerosis)[mh] OR (((multiple or disseminated) adj2 scleros*)) OR (encephalomyelitis disseminata) OR (MS)[Title] OR (Myelitis, Transverse)[mh] OR (transverse myelitis) OR (Demyelinating Diseases)[mh] OR (Demyelinating Autoimmune Diseases, CNS)[mh] OR ((Demyelinat* adj2 (syndrome* or disease* or autoimmun*))) OR ((Chronic Cerebrospinal Venous Insufficiency or CCSVI)) OR (venous insufficiency)[mh] OR ((Devic* adj (disease or syndrome))) OR (((clinical* isolat* or radiological* isolat*) adj2 syndrome*)) OR (optic neuritis)[mh] OR (((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*))) OR ((NMO or NMOSD))

2

3

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of pharmacological management of spasticity in MS



Appendix D – Effectiveness evidence

D.1 Baclofen versus placebo

Table 17: ORSNES 2000

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Orsnes GB, Sorensen PS, Larsen TK, Ravnborg M. Effect of baclofen on gait in spastic MS patients. Acta Neurol Scand 2000; 101: 244-248	Placebo controlled cross-over double blind trial. No details of randomisation or allocation concealment. Double blinding clear but assessor blinding not clear.	14. 1 person withdrew for non-medical reasons during first part of study (group to which he/she belonged at the time is not given)	5/14 male; aged 24-57 (median 42); clinically definite MS and stable disease for at least 1 month; median EDSS of 5 (range 3.5-6); median NRS of 67 (range 57-80); median MSIS 32 (range 17-51); median ambulation index 3 (range 2-3); median Ashworth score 0.8 (range 0-2); 5 secondary progressive, 5 relapsing remitting, 4 primary progressive; all had moderate functional deficits, able to walk unaided for at least 3min; spasmolytics withheld for 1 week before entering study and alcohol was not consumed 12 h before the tests. No	Oral baclofen. Starting dose was 5 mg 3x per day with a dose escalation of 5mg every 3 days to 15 mg 3x per day, as tolerated. The max dosage continued for 11 days and then assessments made, and dose tapered over the following 7 days. Wash-out period of 2 weeks.	Identical placebo	18 days	Muscle tone tendon reflexes EDSS Ambulation index NRS MSIS gait postural stability	Not stated

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			spasticity-affecting drugs taken.					

Results:

	Baclofen	Placebo	p
Total tendon reflexes ("summation of patellar and Achilles reflexes") – very similar at baseline [13.6 (2.8) for baclofen and 13.7(3.5) for placebo].	11.7(4.1)	13.1(3.1)	0.14 (adjusted for slight baseline differences and period effects)
Muscle tone in knee joint – rather different at baseline [1.9 (1.5) for baclofen and 3.1(2.1) for placebo]	2.8(2.4)	3.292.3)	0.33 (adjusted for baseline difference and period effects)
EDSS, ambulation index, NRS, MSIS	No significant differences reported but no data given.		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Self evaluation of gait	5/13 reported improvement 3/13 reported deterioration 5/13 reported unchanged gait		4/13 reported improvement 9/13reported an unchanged gait					
Adverse events (included fatigue, dizziness, GI effects etc)	9/13		1/13					
Postural stability - sway with closed eyes (cm 10^{-B})	229(70) [13]		223.2(88.8)	0.86				
Postural stability - sway with open eyes(cm 10^{-B})	136(31.5)		134(39.1)	0.20				
Gait	Details of gait parameters given, but unlikely these will be meaningful in the review. The results summary is potentially more useful: During treatment with baclofen te vertical unsteadiness of the right leg was reduced significantly (p=0.04). 10 patients improved during							

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			baclofen and 5 patients improved during placebo treatment. All other parameters showed no significant change when tested in the cross-over design.					

Table 18: BRAR 1991

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Brar SP, Smith MB, Nelson LM, Franklin GM, Cobble ND. Evaluation of treatment protocols on minimal to moderate spasticity in multiple sclerosis. Arch Phys	Double blind, placebo controlled randomised cross-over study. Patients randomised into three possible sequences of the 4 treatments (see comparison	38 subjects recruited but 30 completed the study. 8 drop outs were due to axacerbation of symptoms (n=4), transportation	9 men and 21 women; Ages 24-54 Inclusion: Clinically definite MS; 5.5 or less on the EDSS; clinically stable for 3 months; mild to moderate spasticity. Exclusion: systemic disorders; impaired mentation; previous intolerance to baclofen. Baseline characteristics: reported to be comparable	Baclofen alone – 20 mg per day as a maximum dose, starting at 5mg (though this is unclear) and increasing as tolerated in 5mg increments every day for 5 days. Maximum dosage was maintained for 7 days, making a total	Placebo, as for intervention Also baclofen and stretching, as well as placebo and stretching, but those results not included in	12 days	Ashworth scale Function, as measured by the Minimal Record of Disability (MRD).	None stated.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
med Rehabil 1991; 72: 186-189	column). The location of the placebo treatment in these sequences is not always clear; in any event it appears that more patients would have had baclofen before placebo, regardless of randomisation.	difficulties (n=20, conflict with employment (n=10 and medication side effects(n=1). All drops outs were women.		treatment duration of 12 days.	this summary.			

Results:

	Baclofen	placebo				
quadriceps spasticity (measured on a cybex isokinetic dynamometer)	approx 1 degree increase in flexion range compared to baseline	approx 4 degree decrease in flexion range compared to baseline	NB data were extrapolated from a low resolution figure.			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Patients showing improvement in ambulating 100 yards	3/30	5/30						
Patients showing improvement in climbing stairs or kerbs	6/30	4/30						
Patients showing improvement in household activities	5/30	6/30						
Patients improving in Ashworth scale	9/30	6/30						

Table 19: SACHIAS 1997

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SACHAIS	RCT double blind Multicentre	N=166 randomised and safety analysis N=85 baclofen n=81 placebo N=106 completers and analysed efficacy n=54 baclofen n=52 placebo	Inclusion: Inpatients or outpatients at least 18 yrs old with spasticity secondary to multiple sclerosis. Not receiving any muscle relaxant, ant hypertensive or psychoactive drugs seven days prior to start of study Exclusion: People with evidence or a history of renal, hepatic, or active gastrointestinal disease, clinically evidence joint contractures, psychiatric illness unrelated to multiple sclerosis, seizure disorders, drug or alcohol abuse or clinically significant lab abnormalities Baseline characteristics:	Baclofen 75% 70 to 80 mg	Placebo	5 wks	Neurological exam – check which outcomes to extract Physician global impressions. Degree of change (marked (5) to worse (0) Patient self-evaluation. Rated condition 0 (little of the time) to 3 (all the time)	None reported

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Baclofen n=54	Placebo n=52					
			Male n	23	20					
			Age mean yrs	43	43					
			White n	49	48					
			Inpatient n	8	6					
			Duration of disease mean yr	11	11					
			Type of paralysis							
			Quadraplegia	10	5					
			Paraplegia	30	33					
			Hemiplegia	6	3					
			Other	8	11					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Results:								

		Baclofen n=54			**Placebo n=52**	
	Mean score	Standard error	Difference from baseline to final visit	Mean score	Standard error	Difference from baseline to final visit
Global disease severity Baseline Final	3.91 3.65	0.15 0.14	-0.26	3.96 3.77	0.15 0.13`	-0.19
Physician's assessment of clinical change	Final visit (weighted mean score)					
	Baclofen	**Placebo**	**P**			
Overall spastic state	3.02 N=52	2.37 N=52	<0.001			
Daytime spasms	2.88 N=43	2.23 N=44	<0.025			
Nighttime spasms	2.85 N=40	2.29 N=45	<0.025			
Pain or stiffness	2.69	2.26	<0.025			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	N=52	N=50						
Muscle strength	2.07 N=54	2.21 N=52	Not specified					
Sleeping	2.22 N=50	2.14 N=51	Not specified					
	Baclofen **n=85**	**Placebo** **n=81**	Top five					
Somnolence n	60	29						
Vertigo	19	8						
Excessive weakness	17	9						
Headache	10	7						
Nausea	14	5						

Table 20: SAWA1979

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SAWA1979	Randomised crossover trial	Randomised N=21 Completers n=18	Patients with clinically definite MS or chronic myelopathy (presumed MS). Inclusion: Exclusion: Baseline characteristics: Fifteen male and six female. Mean duration of illness in the males and females was fourteen and none years, respectively	Baclofen Maximum 60 mg Concomitant medication: Drugs such as diazepam or steroids that could affect muscle tome were stopped at least seven days prior to entering the trial	Placebo	End of treatment (time not specified)	Spasticity (0=no spasticity to 5=Significant force required to overcome extensor spasticity) Adverse events	None reported

Results:

	Baclofen n=18	Placebo n=18				
Mean grade of spasticity Baseline End of treatment	 3 2	 3 3				
Detectable change in spasticity	13					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Drop-outs due to side effects		1/21	0/18					
Reporting at least one side effect		15/21	4/21					
Weakness		3/21	0/21	Top five				
Exacerbations of MS		1/21	1/21					
Sedation		6/21						
Mood changes		4/21						
Nausea		5/21						

D.2 Tizanidine versus placebo

Table 21: UKTTG1994

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
UKTTG. A double blind placebo controlled	Double blind randomised placebo controlled	187 randomised. 94 randomised	Inclusion: 18-75yrs; spasticity secondary to clinically definite MS; stable disease during the previous 1 month; no	Tizanidine starting at 2mg daily, with meals, with a 3	Identical placebo	14 weeks	Change in summed muscle tone score	Unclear, but two involved research

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>trial of Tizanidine in the treatment of spasticity caused by multiple sclerosis. Neurology 1994; 44: S70-S78</td><td>trial. Stratified by severity (Ashworth). No details given of randomisation process, nor evidence of allocation concealment. Double blinding clear. Assessor blinding not clear.</td><td>to tizanidine and 93 to placebo.

29/94 in Tizanidine group discontinued prematurely 4 to 90 days after starting the study – 12 because of adverse events and 12 because of patient perception of lack of efficacy, 5 for other reasons.

22/93 placebo patients discontinuing 4-90 days</td><td>concomitant neurologic illness likely to alter muscle tone.

Exclusion: Immunosuppressants prescribed in past month or corticosteroids prescribed during the previous 3 months; patients refusing to discontinue muscle-relaxant meds 1 week before entry; systolic bp> 180mmHg, diastolic >120 mmHg; systolic < 90 mmHg, diastolic < 60 mmHg; systemic disease; laboratory test abnormalities; active bedsores, infection or contractures.

Baseline characteristics very similar:

<table><tr><th></th><th>Tizanidine</th><th>Placebo</th></tr><tr><td>disease duration (mo)</td><td>153(86)</td><td>157(95)</td></tr><tr><td>spasticity</td><td>73(52)</td><td>73(54)</td></tr></table></td><td>week titration phase up to the maximum tolerated dose. The maximum tolerated dose was then continued for a final 9 weeks. In a subsequent week the dose was tapered to zero.

Mean dose taken at commencement of the stable phase was 30.7 mg/day. This dropped to 25.2 mg/day at completion.</td><td>Mean dose taken at commencement of the stable phase was 35 mg/day. This dropped to 33.6 mg/day at completion.

Number of patients in whom muscle tine decreased during the study by at least 1 point

Muscle strength change over course of study</td><td></td><td>muscle strength

spasms

deep tendon reflexes

timed walk

function

upper limb function

comfort

sleep

AES</td><td>er/authors were employees of Sandoz pharma Ltd, who manufacture Tizanidine. Hence there is a likely conflict of interest.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		after starting the study, 13 due to lack of efficacy, 5 due to adverse events and 4 for other reasons. ITT was used as the primary analysis, with last available result used as the imputation method.	duration (mo)				Change in frequency of spasms over course of study Change in deep tendon reflexes throughout study Change in timed walking (8m) (s) throughout study Patients with improved intermediate functions Patients with improved			
			stable spasticity duration (mo)	36(41)	37(43)					
			Mild/mod/severe spasticity	37/48/9	43/40/9					
			motor deficit duration (mo)	80(76)	77(69)					
			clin def/lab supp/prob MS (numbers)	51/31/12	51/27/15					
			Age	47(9)	47(9)					
			F:M	1.7	2					

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							upper limb function Patients with improved comfort Patients with improved sleep quality investigator assessment of efficacy – good or very good investigator assessment of tolerability – good or very good			
Results										

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Tizanidine (n=94)	**Placebo (n=93)**	**p**			
Change in summed muscle tone score (Ashworth) from baseline (sd of change not available but we have the p value for the comparison which will allow its estimation)			3.9 baseline 18.5(9.4) post test 14.6(10.1)	1.5 baseline 16.8(11.1) post test 15.3(9.9)	0.004 (the sds for each group were calculated before entry into revman)			
Number of patients in whom muscle tine decreased during the study by at least 1 point			67/94	46/93	<0.005 (the sds for each group were calculated before entry into revman)			
Muscle strength change over course of study			+2.2 (no sd available) baseline 71(16.2) post 73.2(15.5)	+2.2(no sd available) baseline 72.2(14.1) post 74.4(13.2)	No p values/CIs so not able to calculate sd of changes (thus cannot analyse in rev man)			
Change in frequency of spasms over course of study			-0.8(no sd available) baseline 6.3(6.6) post 5.5(7)	-0.8(no sd available) baseline 5.2(5.8) post 4.4(6)	No p values/CIs so not able to calculate sd of changes (thus cannot analyse in rev man)			
Change in deep tendon reflexes throughout study			-1.6(no sd available) baseline 18.1(7.1) post 16.5(7.1)	-0.7(no sd available) baseline 17.4(6.5) post 16.7(6.8)	No p values/CIs so not able to calculate sd of changes (thus cannot analyse in rev man)			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Change in timed walking (8m) (s) throughout study			+0.9(no sd available) baseline 20.3(19.7) post 21.2(34.5)	-2.9(no sd available) baseline 27.9(31) post 25(26.3)	No p values/CIs so not able to calculate sd of changes (thus cannot analyse in rev man)			
Patients with improved intermediate functions			18/89	9/89				
Patients with improved upper limb function			5/87	4/88				
Patients with improved comfort			31/79	12/83				
Patients with improved sleep quality			18/42	15/45				
investigator assessment of efficacy – good or very good			22/91	6/93				
investigator assessment of tolerability – good or very good			38/91	79/93				
patient assessment of efficacy – good or very good			25/89	13/93				
patient assessment of tolerability – good or very good			36/89	79/93				
Patients reporting AEs			82/94	57/93				
Numbers discontinuing because of AEs			12/94	5/93				

Table 22: SMITH1994

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SMITH1994	RCT double blind 14 centres USA	N=256 (treated/evaluated) N=220 (analysed) Tizanidine n=111 Placebo n=109	Inclusion: People aged 18 to 70 yrs with stable spasticity secondary to MS. Spasticity had to be severe enough to cause significant discomfort or functional impairment and to produce a minimum score of on the Ashworth Scale or a minimum of 2 in the muscle spasm type and frequency score in the most severely affected muscle group People receiving antispastic therapies discontinued for at least 2 wks before baseline data collected. Exclusion: People on muscle-relaxant drugs. People experiencing an acute relapse. People with fibrous contractures. Baseline characteristics:	Tizanidine	Placebo	12 weeks	Ashworh Scale Spasms and clonus (patient diary) Transformed to a risk ratio -0.33 equiv to -50% change. Median used (data still skewed) Global efficacy and tolerability Adverse events	Athena Neurosciences Inc, the drug's sponsor in the US and was co-ordinated by Bio-Pharm Clinical Services Inc

	Tizanidine n=111	Placebo n=109

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Male %	36	39					
			Age yrs mean (SD)	46.1 (9.6)	44.5 (9.4)					
			MS spasticity score %							
			Ashworth 1 or 2	28	21					
			Ashworth 3	60	65					
			Ashworth 4	22	23					
			Duration of MS mean (SD)	129.9 (92.9)	133.8 (99.3)					
Results:										

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Tizanidine n=105	**Placebo n=104**						
Ashworth Scale Baseline mean Change from baseline mean adj (SD)	 12.99 -2.03 (7.33)	 14.95 -2.73 (7.17)	P=0.460					
	Tizanidine	Placebo						
Response ratio % change from baseline median At titration n tizanidine/placebo 91/94	 -33.33	 -25.37	These data were skewed and so only medians were the relevant data presented in the paper. These cannot be entered into revman					
End point n tizanidine/placebo 100/98	 -61.11	 -40.96	These data were skewed and so only medians were the relevant data presented in the paper. These cannot be entered into revman.					
	Tizanidine	Placebo	P					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Global efficacy and tolerability Physician/prescribed Patient Physician/assessor			Sds calculated from p values. 0.043 0.011 NS					
No. reporting at least one adverse event	101/111	66/109						
Body as a whole	59/111	34/109						
Cardiovascular system	11/111	3/109						
Digestive system	28/111	12/109						
Metabolic and nutritional	8/111	6/109						
Musculoskeletal	10/111	12/109						
Nervous system	93/111	41/109						
No statistically significant differences were noted for clonus, type and frequency of muscle spasms, functional capacity (walking time and activities of daily living) and muscle strength Two significant adverse events (drug-induced hepatitis and hallucinations)								

Table 23: LA PIERRE1987

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lapierre1987	RCT double blind Montreal (?)	N=66 randomised N=59 completers Tizanidine n=28 Placebo n=31	Inclusion: People aged 18 to 60 yrs with a definite diagnosis of multiple sclerosis and at least a moderate degree of spasticity, severe enough to interfere with functional performance in everyday life. Their spasticity had to be stable for at least two mths Exclusion: Patients with active infections, severe contracture or evidence of hypertension, cardiac disease, malignancy or any disease involving a major organ Baseline characteristics:	Tizanidine Mean daily dose (end of maintenance) (SEM) 18.4 (1.2)	Placebo Mean daily dose (end of maintenance) (SEM) 22.5 (1.2)	8 weeks	Ambulation index (EDSS) Upper extremity index Disability status (Kurtke) Total limb tone	None reported

	Tizanidine	Placebo
Male %	48	52

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Age yrs (SEM)	47.6 (1.4)	43.8 (1.6)					
			Severity of spasticity Mild Moderate Severe	 3 21 8	 2 20 11					
Results:										

	Tizanidine		Placebo			
Mean (SEM)	Baseline	Day 56	Baseline	Day 56		
Disability status	5.07 (0.29)	5.07 (0.28)	4.90 (0.34)	4.90 (0.34)	Lower scores better	Baseline unequal and no variance for change scores/p values, so entry into rev man not possible
Ambulation index	4.22 (0.40)	4.11 (0.41)	4.61 (0.43)	4.61 (0.44)	Lower scores better	Baseline unequal and no variance for change scores/p values, so entry into rev man not possible

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Upper extremity index	0.52 (0.14)	0.48 (0.14)	0.52 (0.14)	0.52 (0.14)	Lower scores better	As baseline values equal was able to add post test scores into rev man		
Total limb tone	23.89 (1.32)	27.75 (1.60)	29.80 (1.80)	31.29 (1.74)		Baseline unequal and no variance for change scores/p values, so entry into rev man not possible		

D.3 Tizanidine versus baclofen

Table 24: HOOGSTRATEN1988

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hoogstraten et al. Tizanidine versus baclofen in the	Randomised cross-over study. Blinding only for assessor	16. 14 completed the cross-over and 11 completed	6 women and 10 men, aged 34-67, with spasticity due to MS. Inclusion: stability of spasticity for at least 2 months prior to the study; EDSS 4-7.	Baclofen. Dose not given, but stated that it was fixed based on the “response to and tolerance	Tizanidine Dose not given, but stated that it was fixed based on	7-9 weeks	EDSS Incapacity status Ambulation index	Medical Research Department of SANDOZ BV,

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
treatment of spasticity in multiple sclerosis patients. Acta Neurol Scand 1988; 77: 224-230.	and patient, not HCP.	both treatment periods. The 3 who did not complete both all withdrew from baclofen in the second period. 14 were included in the data presented (though the paper's own analysis did 2 analyses: 1) they omitted these 3 from the cross-over	Exclusion: severe cardiac insufficiency; marked hypertension (diastole > 110mgHg); severe hypotension; chronic alcoholism; history of mental illness; pre-treatment with diazepam or dantrolene (if previous baclofen there had to be a 3 day washout before commencing the study)			of treatment". Ranged from 15-60 mg daily Duration: 2-3 weeks of an initial titration phase, 4 weeks at the fixed dose, then 1-2 weeks of gradual discontinuation. 3 days washout.	the "response to and tolerance of treatment". Ranged from 12-24 mg daily Duration: 2-3 weeks of an initial titration phase, 4 weeks at the fixed dose, then 1-2 weeks of gradual discontinuation. 3 days washout.		Ashworth scale spinal reflexes clonus spasms Isometric muscle strength Adverse events	Netherlands. This is a pharmaceutical company, involved in the manufacture of Tizanidine. Hence a possible conflict of interest exists.

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		analysis, and 2) they just observed results from the first period)								
Results: the authors performed two analyses for “overall efficacy” : 1) they omitted the 3 who dropped out from the baclofen arm of the cross-over analysis, and 2) they just observed results from the first period. In both analyses, there was no significant difference between groups. Although the latter analysis was clearly inappropriate (as it was not decided a priori and thus prone to post hoc bias), the former analysis was essentially an available case analysis. The result for this showed a mean difference (95% CIs) for baclofen v tizanidine of 0.5(-0.2, 1.2) [direction of point estimate favouring baclofen though clearly there was large uncertainty in the true population direction of effect]. For each group, +1 or -1= slight improvement/deterioration, +2 or -2 = moderate improvement/deterioration and +3 or -3= marked improvement/deterioration, based on changes from pre to post, and so the paired differences also relate to this scale. However it is the categorical analysis (see third column in results section below) that has been entered into GRADE, as this is not subject to problems arising from a non-interval grading system, and likely non-parametric distributions.									
						paired mean difference (sd) (Baclofen vs Tizanidine)	**Categorical analysis, coded as 1= worse or no better (event) and 0 = better (non-event).**				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					This was analysed using Mantel Haenszel method for paired data.			
Spasticity (For each group, +1 or -1= slight improvement/deterioration, +2 or -2 = moderate improvement/deterioration and +3 or -3= marked improvement/deterioration, based on changes from pre to post, and so the paired differences also relate to this scale).				0.36(0.92) Se=0.109	1 in both=3 1 in bac only=1 1 in Tiz only =2			
Spasms (For each group, +1 or -1= slight improvement/deterioration, +2 or -2 = moderate improvement/deterioration and +3 or -3= marked improvement/deterioration, based on changes from pre to post, and so the paired differences also relate to this scale).				0.55(1.13) Se=0.341	1 in both=2 1 in bac only=1 1 in Tiz only =4			
Mobility (For each group, +1 or -1= slight improvement/deterioration, +2 or -2 = moderate improvement/deterioration and +3 or -3= marked improvement/deterioration, based on changes from pre to post, and so the paired differences also relate to this scale).				0.09 (0.70) Se=0.211	1 in both=9 1 in bac only=2 1 in Tiz only =0			
Adverse events				**Baclofen**	**Tizadinine**			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
subjective muscle weakness				11	4			
somnolence				4	8			
dry mouth				2	5			
flushes				1	3			
nausea				3	2			
depression				1	2			
incontinence				3	1			
bladder retention				0	1			
dizziness				2	2			
blurred vision				1	0			
headache				1	0			
dysarthria				1	1			
burning hands/feet				1	0			
sleep disturbance				0	2			
Muscle (isometric) strength (paired data not available) Mean change from baseline in Newtons (sd)				**Baclofen**	**Tizadinine**			
Hip flexors				**0.6 (19.7)**	**4(16.8)**	NS		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
knee extensors				**-2.8 (20.8)**	**-2(23.3)**	NS		
knee flexors				**0.1 (40)**	**5.1(17.5)**	NS		
dorsiflexors				**3.3 (22.7)**	**-8.2(30.8)**	NS		
plantar flexors				**-2.5 (52.4)**	**5.4 (31.2)**	NS		

Table 25: EYSSETTE1988

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
EySSette M, Rohmer F, Serratrice G. Multi-centre, double blind trial of a novel	Multi-centre double-blind randomised trial.	100. Withdrawals before 2 weeks 1 patient withdrew in each group weeks because of side effects.	Inclusion: Male or female; 18-70 years; spaticity due to MS All antispastic Rx, including benzodiazepines, was discontinued 3 days before entry to the trial. Baseline characteristics: Variance given as SE	Initial dose of 6mg tizanidine (3 capsules per day). The dose was increased, if tolerated, by	Initial dose of 15mg baclofen (3 capsules per day). The dose was increased, if tolerated, by	2 and 8 weeks after start of Rx	locomotor function flexor spasms Muscle tone	None stated.

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. Current medical Research and Opinion 1988; 10: 699-708.	No details of randomisation and no evidence of allocation concealment. No mention of any blinding.	<u>Withdrawals between 2 and 8 weeks of treatment</u> In Tizanidine group 3 withdrew because of side effects and 4 because of lack of efficacy. In the Baclofen group 3 patients withdrew because of side effects, 1 because of lack of efficacy and 1 for reasons unrelated to treatment. Unclear which (if any) of these treatment withdrawals returned for follow up. Results section unclear on		Tizanidine (n=50)	Baclofen (n=50)	1 capsule every 2 days during the first 2 weeks of the study to a maximum dose of 24mg (12 capsules). Patients were then treated with their optimum dose for a further 6 weeks, making a total treatment period of 8 weeks.	1 capsule every 2 days during the first 2 weeks of the study to a maximum dose of 60mg (12 capsules). Patients were then treated with their optimum dose for a further 6 weeks, making a total treatment period of 8 weeks.		Clonus Muscular strength Difficulties with bladder control	
			Male	56%	58%					
			mean age (SE)	46.8(1.6)	47.5(1.7)					
			Wt (kg)	63.6(1.8)	63.4(1.5)					
			Ht (cm)	165.8(1.2)	165(1.1)					
			Mean duration of gait disturbance (yrs)	10.8	13.4					

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		this as denominators sparingly reported. No ITT analysis reported. There is therefore some risk of attrition bias, as there is a differential (6%) rate of loss due to treatment [8/50 compared to 5/50]								
Results:										
	Tizanidine	**Baclofen**								
Development of new ability to ambulate at 8 weeks (expressed as a proportion of those unable to ambulate at baseline)	2/33	0/37								
Development of new ability to transfer	17/35	13/33								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
to/from bed/wheelchair at 8 weeks (expressed as a proportion of those unable to ambulate at baseline)								
Improvement in flexor spasms at 8 weeks (expressed as a proportion of those with flexor spasms at baseline)		20/36	14/33					
No change or deterioration of overall clinical status after 2 weeks of treatment		17/49	13/49					
No change or deterioration of overall clinical status after 8 weeks of treatment		8/41	18/44					
Overall evaluation of efficacy – patients		9/50	11/50					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
stating treatment was ineffective at end of study								
Overall evaluation of tolerability – patients stating treatment was poorly tolerated		6/50	4/50					
adverse events - daytime drowsiness		15/50	10/50					
adverse events - fatigue		8/50	12/50					
Discontinuation due to adverse events		6/50	4/50					
Improvement in forearm flexor stretch reflex at 8 weeks (out of those with abnormality at baseline)		12/18	16/28					
Improvement in quadriceps stretch reflex at 8 weeks (out of those with		22/35	13/28					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
abnormality at baseline)								
Improvement in knee flexor stretch reflex at 8 weeks (out of those with abnormality at baseline)		19/33	17/34					
Improvement in triceps surae stretch reflex at 8 weeks (out of those with abnormality at baseline)		15/33	19/38					

Table 26: SMOLENSKI1981

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td rowspan="6">Smolenski C, Muff S, Smolenski-Kautz S. A double-blind comparative trial of a new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Current Medical research and opinion 1981; 7: 374-383</td><td rowspan="6">Double blind RCT.

No details given on randomisation, allocation concealment or blinding.</td><td rowspan="6">21. No withdrawals reported, and specifically stated that none withdrew due to adverse events.</td><td colspan="3">Inclusion: Hospitalised patients with MS; spasticity stable for at least 2 months prior to the start of the trial.

Exclusion: History or evidence of cardiac, renal or hepatic disease, severe hypertension, epilepsy, chronic alcoholism, diabetes mellitus, overy psychopathology.

Baseline characteristics: described as similar.</td><td rowspan="6">Initial daily dose of 4mg tizanidine (in 2 daily capsules). The dose was increased, if tolerated, during the first few weeks of the study to a optimum dose of 3-6 capsules/day in 3 divided doses. The total treatment period was 6 weeks.</td><td rowspan="6">Initial daily dose of 10mg baclofen (in 2 daily capsules). The dose was increased, if tolerated, during the first few weeks of the study to a optimum dose of 3-6 capsules/day in 3 divided doses. The total treatment period was 6 weeks.</td><td rowspan="6">6 weeks (end of treatment)</td><td rowspan="6"></td><td rowspan="6">None stated</td></tr>
<tr><td></td><td>Tizanidine (n=11)</td><td>Baclofen (n=10)</td></tr>
<tr><td>Male</td><td>5/11</td><td>5/10</td></tr>
<tr><td>mean age</td><td>53(11)</td><td>55(10)</td></tr>
<tr><td>mean duration of signs (years)</td><td>17.3(10)</td><td>26.6(8)</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Severe spasticity	6/11	6/10					
			Quardriparesis	4/11	5/10					
			quadrriplegia	4/11	7/10					

Results:

	Tizanidine	Baclofen				
left leg muscle tone at 6 weeks - no change or worse	3/11	1/10				
Right leg muscle tone at 6 weeks - no change or worse	5/11	2/10				
left foot muscle tone at 6 weeks - no change or worse	3/11	2/10				
Right foot muscle tone at 6 weeks - no change or worse	2/11	2/10				
left leg flexor spasms at 6 weeks – no change or worse	2/11	3/10				
right leg flexor spasms at 6 weeks – no change or worse	3/11	2/10				
left leg extensor spasms at 6 weeks – no change or worse	2/11	2/10				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
right leg extensor spasms at 6 weeks – no change or worse				2/11	1/10			
left leg abductor spasms at 6 weeks – no change or worse				5/11	3/10			
right leg abductor spasms at 6 weeks – no change or worse				3/11	2/10			
Physio assessed function -improvement (-ve indicates deterioration) in turning in bed.				1	0.5			
Physio assessed function -improvement (-ve indicates deterioration) in sitting balance.				1	0.4			
Physio assessed function -improvement (-ve indicates deterioration) in lying-sitting.				0.1	-0.2			
Physio assessed function -improvement (-ve indicates deterioration) in standing/sitting				0.6	0			
Physio assessed function -improvement (-ve indicates deterioration) in personal toilet.				0.3	-0.2			
Physio assessed function -improvement (-ve indicates deterioration) in walking distance.				0.7	0			
Physio assessed function -improvement (-ve indicates deterioration) in walking ability.				0.3	-0.05			
Physio assessed function -improvement (-ve indicates deterioration) in managing stairs				0.6	-0.1			
Physicians global assessment of patients who are no better or worse (proportion) in overall spastic state				1/11	1/10			
Physicians global assessment of patients who are no better or worse (proportion) in daytime spasms				2/11	4/10			
Physicians global assessment of patients who are no better or worse (proportion) in night-time spasms				3/11	3/10			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Physicians global assessment of patients who are no better or worse (proportion) in clonus activity				6/11	5/10			
Physicians global assessment of patients who are no better or worse (proportion) in walking				8/11	7/10			
Physicians global assessment of patients who are no better or worse (proportion) in dressing/undressing				9/11	10/10			
Overall assessment of physician of the efficacy (moderate or poor)				4/11	2/10			
Overall assessment of patient of the efficacy (moderate or poor)				5/11	3/10			
adverse events - tiredness				5/11	0/10			
adverse events – weakness				2/11	3/10			
adverse events – dry mouth				1/11	1/10			
adverse events – ataxia				1/11	1/10			
adverse events – nausea				0/11	1/10			
adverse events – pyrosis				0/11	1/10			

Table 27: BASS1988

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
BASS1988	Randomised cross-over trial double blind Single centre USA	N=66 randomised n=48 completers and analysed Tizanidine then baclofen n=28 Baclofen then tizanidine n=20	Inclusion: People with clinically definite MS with spasticity that interfered with activities of daily living. Spasticity was stable for two mths. Exclusion: Baseline characteristics:	Tizanidine Mean 17.4 (SD/SE 1.6) mg	Baclofen Mean 34.9 (SD/SE 3.2) mg	8 wks	Overall evaluation – efficacy assessment Adverse events	Sandoz Canada

	Tizanidine then Baclofen N=32	Baclofen then tizanidine N=30
Males	53%	47%
Age yrs (SEM)	49.7 (2.0)	52.5 (2.2)
Paraperesis	90%	80%

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Status at entry Remitting Progressive Stable	 1 8 23	 0 11 19					
			Duration of spasticity mean (SEM)	8.7 (1.1)	7.5 (0.7)					
			Severity Mild Mild/moderate Moderate Moderate/severe Severe	 3 0 20 2 7	 3 1 14 3 9					
			Previous treatment for							

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			spasticity							
			Baclofen	14	14					
			Diazepam	6	4					
			Dantrolene	1	1					
			Cyclobenzaprine	1	0					
			Orphenadrine	0	1					

Results: Overall evaluation – Efficacy assessment

		Tizanidine			**Baclofen**	
	Poor/fair	Good	Excellent	Poor/fair	Good	Excellent
Patient	41/54	11/54	2/54	31/51	17/31	3/31
Investigator	33/54	10/54	1/54	30/50	16/50	4/50
Physiotherapist	38/52	13/52	1/52	30/50	15/50	5/50
	Tizanidine	**Baclofen**				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Discontinued due to AEs	4/32	11/30						
Muscle weakness	11/32	17/30	Total n might be wrong					
Somnolence	15/32	9/30						
Dry mouth	12/32	7/30						
Spasms	8/32	2/30						

Table 28: STIEN1987

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
STIEN1987	RCT double blind multicentre Norway	N=40 randomised N=38 completers N=19 tizandine	Inclusion: People with definite MS. All were residents at a nursing homes for neurological patients. They had all been in a stable phase for 3 mths prior to the trial.	Tizandine n=23 mg All previous anti-spasticity medication was withdrawn	Baclofen 59 mg All previous anti-spasticity medication was withdrawn	6 wks	Neurological disability – Kurtzke Functional assessment – Pedersen Muscle tone – Ashworth	None reported

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td>N=19
baclofen</td><td>Exclusion:

Baseline characteristics:
<table><tr><td>n</td><td>Tizanidine n=18</td><td>Baclofen n=20</td></tr><tr><td>Male %</td><td>50%</td><td>40%</td></tr><tr><td>Age median yrs</td><td>50</td><td>45</td></tr><tr><td>Disease duration median</td><td>14</td><td>13</td></tr><tr><td>Spasticity
Mild
Moderate
Severe</td><td>
4
9
5</td><td>
2
8
10</td></tr></table></td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Paresis Paraplegia Quadriparesis/quadriplegia	10 8	8 12					
Results:										

	Improvement		No change		Worse	
	Tizanidine	Baclofen	Tizanidine	Baclofen	Tizanidine	Baclofen
Provoked or spontaneous muscle activity	12/18	13/20	5/18	5.20	1/18	2/20
Muscle strength	2/18	2/20	15/18	15/20	1/18	3/20

	Physician		Patients			
	Tizanidine	Baclofen	Tizanidine	Baclofen		
Good	2	4	1	6		
Moderate	12	11	8	6		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Poor	4	5	9	8				
	Tizandine	Baclofen						
Drop-outs (poss due to adverse events	1/20	1/20	Report states one person in each group dropped out but n18 tizandine n=20 baclofen					
Tiredness, muscular weakness, sleepiness and/or dry mouth	6/18	5/20						

D.4 Baclofen versus diazepam

Table 29: ROUSSAN1997

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roussan M, Terrence C, Fromm G. Baclofen versus diazepam for the treatment of spasticity and long term follow-up of baclofen therapy. Pharmatherapeutica 1985; 4: 278-284	Double blind **cross-over** study	6 (13 in study, but other 7 had other diagnoses, and so not included here).	3 male and 3 female. Mean age 47; mean duration of spasticity 10.8 yrs. Inclusion: Adult patients with spasticity for at least 3 months prior to start of study;	Baclofen 5mg 3x per day with meals for 5 weeks, followed by 3 week washout period. Dose adjusted at discretion of physician-observer but maximum allowable dose was 80mg per day. Mean was 47.3 (range 25 to 60) daily.	Diazepam 2mg 3x per day with meals for 5 weeks, followed by 3 week washout period. Dose adjusted at discretion of physician-observer but maximum allowable dose was 40mg per day. Mean was 28 (range 10 to 40) daily.	5 weeks		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Results: These results were not amenable for ref man as they were mutually exclusive categories by virtue of the nature of the question – which of the *two* was better?								
Better patient rated global response with diazepam	3/6							
Better patient rated global response with baclofen	1/6							
No difference in patient rated global response	2/6							
Better physician rated global response with diazepam	2/6							
Better physician rated global response with baclofen	3/6							
No difference in physician rated global response	1/6							
	Diazepam	**Baclofen**						
Adverse events - drowsiness	3/6	1/6 (also drowsy with diazepam)						
Adverse events – loss of erection	1/6	1/6 (also loss of erection with diazepam)						
Adverse events – leg oedema	0/6	1/6						

Table 30: FROM1975

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
FROM1975	Randomised crossover trial	Randomised: N=17 Completers: n=16	Inclusion: Inpatients with spasticity due to multiple sclerosis Exclusion: Baseline characteristics: 6 male and 10 female. Mean age 51 yrs (range 38 to 68). Mean duration of illness 17.5 yrs (range 3 to 40 yrs)	Baclofen Mean daily dose 61.2 mg (range 30 to 120)	Diazepam Mean daily dose 26.8 mg (range 10 to 40)	4 weeks per treatment	Lower limb spasticity (Ashworth)	

Results:

	Baclofen (n=16)	Diazepam (n=16)				
Lower limb spasticity (Ashworth) Baseline Decrease at end of treatment	 76 55	 80 57				
			Effect of treatment			
	Patients with flexor spasms before treatment	**Improved**	**Unchanged**	**Worse**		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Baclofen (n=16)	12	10	1	1				
Diazepam (n=16)	14	12	1	2				
	Baclofen (n=16)	**Diazepam (n=16)**						
No. of limbs with clonus	26	28						
	Baclofen (n=16)	**Diazepam (n=16)**	Top five					
No. of patients experiencing adverse events	8	12						
Sedation	5	11						
Weakness	3	2						
Depression	2	0						
Nausea	2	0						
Euphoria	1	1						

D.5 Tizanidine versus diazepam

Table 31: RINNE1980

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rinne UK. Tizanidine treatment of spasticity in multiple sclerosis and chronic myelopathy. Current therapeutic research 1980; 28: 827-836	Double blind randomised parallel group trial. No mention of methods of randomisation or if allocation concealment was used. No details of double blinding. This paper actually described three trials. The first and third involved chronic myelopathy patients in addition to	30. 4 dropped out of the diazepam treatment group, 1 after 2 weeks and 3 after 4 weeks. However this did not affect analyses, which were on all those randomised.	Inclusion: Multiple sclerosos; stable spasticity for at least 1 year. Baseline characteristics: Reported as similar Tiz (n=15) / Diaz (n=15) male 6/15 5/15 Age 42(3) 40(2) wt 64(3) 6693) ht 172(2) 168(2) Disease duration 7(1) 12(2) Severity mild 1/15 1/15 mod 6/15 7/15 severe 8/15 7/15	Tizanidine for 6 weeks. Maximum daily dose was 18mg in 2mg capsules (in 3 divided daily doses).	Diazepam for 6 weeks. Maximum daily dose was 22.5 mg in 2.5mg capsules (in 3 divided daily doses).	6 weeks	Change in spasticity Adverse events	Signe and Ane Gyllenberg foundation

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	MS patients, and there was no sub-grouping in the results, so this review does not address those. This review only addresses the second trial described.									

Results:

	Tizanidine	Diazepam				
Improvement in spasticity	**9/15**	**9/15**				
Patients tolerating to maximum daily dose	**10/15**	**3/15**				
Adverse events requiring withdrawal	**0/15**	**4/15**				

D.6 Dantrolene versus diazepam

Table 32: SCHMIDT1976

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SCHMIDT1976	RCT crossover double blind USA	N=46 randomised N=42 completers	Inclusion: Outpatients with moderate or severe spasticity which clearly interfered with physical function No ACTH or corticosteroids had been used for at least six mths. Exclusion: Severe dementia, ataxia or tremor Baseline characteristics: None reported	Dantrolene Low dose 25 mg high dose 75 mg both four times daily Muscle relaxants or sedatives discontinued	Diazepam Low dose 2 mg high dose 5 mg both four time daily Walking speed mean score	Two weeks for each dose	Spasticity mean score (no details) Walking speed Improved/deteriorated symptoms	None reported

Results:

	Low dose dantrolene	High dose dantrolene	Control dantrolene	Low dose diazepam	High dose diazepam	Control diazepam
Spasticity mean score	10.00	9.54	10.900	9.40	9.14	10.70

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Walking speed mean score	11.33	10.56	10.82	13.81	17.12	10.73		
		Changes from baseline (no.)						
	A both	B diazepam only	C dantrolene only	Analysed using Mantel Haentzel method for paired categorical outcomes				
Improved								
Cramps, spasms	17	4	8					
Stiffness	10	10	6					
Gait	2	4	5					
Bladder urgency, incontinence	1	1	3					
Dizziness, vertigo	0	1	3					
Strength	0	2	1					
Coordination	0	1	2					
Balance	0	1	1					
Drowsiness	0	0	2					
Deteriorated								
Strength	22	10	6					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Drowsiness	10	18	3					
Gait	18	9	4					
Coordination	2	10	2					
Imbalance	7	8	0					
Fatigue	2	6	3					
Cramps, spasms	2	4	4					
Bladder urgency, incontinence	0	4	5					
Dizziness, vertigo	5	3	3					
Diarrhoea	2	0	4					
Headache, nausea	0	0	1					
Which drug did you prefer? 22/42 dantrolene at a dose of 118 (SD54) mg daily 13/42 diazepam at a dose of 10.1 (SD5.5) mg daily Seven neither drug								

D.7 Dantrolene versus placebo

Table 33: GELENBERG1973

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gelenberg AJ, Poskanzer DC. The effect of dantrolene sodium on spasticity in multiple sclerosis. Neurology 1973; 23: 1313-1315	Triple blind cross-over study. No mention of randomisation, but this presents less risk of selection bias than would occur in a parallel trial, so this paper has been included. Blinding well described.	20. No losses reported.	11 men and 9 women aged 39-67. 14/20 able to ambulate with some difficulty, 5 confined to a wheelchair or bed and one completely disabled by quadriplegia. Inclusion: Clearly established diagnosis of MS complicated by moderate to severe spasticity.	Dantrolene Sodium. Dose initially at 50 mg 4 times per day (200mg per day) and gradually increased, as tolerated, to 800mg per day. Treatment duration was 5 weeks. Washout period of 1-3 weeks.	Placebo in exactly the same doses.	5 weeks	Patient and physician evaluation of efficacy Adverse events	None stated
Results:								
	Dantrolene preference	**Plecobo preference**	**no preference**					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Patient preference	7/20		4/20 (based on side effects)	9/20				
Physician preference	6/20		0/20	14/20				
	Dantrolene		**Placebo**					
adverse events - weakness	15/20		0/20					
adverse events - lightheadedness	11/20		1/20					
adverse events - nausea	7/20		0/20					
adverse events - dizziness	6/20		0/20					
adverse events - diarrhea	6/20		0/20					
adverse events – speech difficulty	4/20		0/20					
adverse events – drowsy/lethargy	3/20		0/20					
adverse events - headache	2/20		1/20					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
adverse events - irritability	2/20	0/20						
adverse events - photophobia	1/20	0/20						
adverse events - depression	1/20	0/20						
adverse events - cramps	0/20	1/20						

Table 34: TOLOSA1975

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
TOLOSA1975	RCT double blind	N=23 N=12 dantrolene N=11 placebo	Inclusion: People with multiple sclerosis Exclusion:	Dantrolene	Placebo	8 wks	Spasticity (0=flaccid, 6= extreme resistance) Weakness Discontinued to due side effects	None reported

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Baseline characteristics: No baseline data reported					
Results:								

	Dantrolene n=12	Placebo n=11				
Reduction in spasticity	5	3				
Weakness	6	1				
Discontinued to side effects	2	0				

D.8 Gabapentin versus placebo

Table 35: CUTTER2000

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cutter NC, Scott DD, Johnson JC, Whiteneck G. Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomised trial. Arch Phys med Rehabil 2000; 81: 164-168	Randomised double blinded placebo controlled cross-over trial. No mention of method of randomisation or evidence of allocation concealment. Double blinding and blinding of assessors was well described.	22 randomised to two groups. One withdrew after one day on gabapentin due to headache. Presumably this was in the first period. No evidence that this patient was included in analysis via ITT analysis.	All had chronic progressive form of MS. All had confirmation of diagnosis from lab/MRI. 90% were men. Inclusion: 18-85 yrs; eligible for care at the veterans medical centre; clinical evidence of spasticity. Exclusion: lack of clinically evident spasticity; inability to attend for periodic evaluation; potential to become pregnant; significant renal dysfunction.	gabapentin. Starting dose of 300mg three times daily (900mg/day), titrated up by 300mg increments every 2 days to a maximal dose of 900mg three times daily (2700mg/day). 14 day washout period and then on to placebo arm	Identical placebo regime. 14 day washout period and then on to Rx arm.	Total study length of 26 days.	EDSS Ashworth scale clonus scale deep tendon reflexes plantar stimulation response patient assessed scales adverse events Digit Span and Digit Symbol portions of the WAIS-R for assessing	Missouri Research Enrichment Program. Denver VAMC (Denver VA Medical centre)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		<10% differential.					concentration / attention	

Results: There was no presentation of the counts of people having events in BOTH arms, which is necessary to assess a paired categorical association; we have correctly paired p values, but these are for chi squares with 3 or 4 categories – hence not possible to apply these p values to pairwise comparisons suitable for a meta-analysis. Much data presented in paper, and results given below are in a summarised form. For almost all variables, the values at baseline (i.e. at the beginning of either of the cross-over arms, whether at the start of the study or the end of the washout period) were very similar across groups, and the degree of this similarity is described below in brackets.

	Gabapentin	Placebo				
Moderate or severe spasms (same at baseline)	3/21	14/21				
Spasms occurring more than once per hour (very similar at baseline)	1/21	7/21				
Painful spasms – moderate or severe (same at baseline)	5/21	13/21				
Spasticity worse or unchanged relative to baseline	6/21	16/21				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Modified Ashworth score - ≥4 (very similar at baseline)	3/21	10/21						
Clonus sustained or spontaneous (similar at baseline)	4/21	8/21						
Spasticity interfering with function – makes function difficult or prevents function (same at baseline)	11/21	17/21						
Response to plantar stimulation – slight knee or hip movement or more (very similar at baseline)	5/21	11/21						
Deep tendon reflexes – brisker than average or very brisk (similar at baseline)	11/21	14/21						
Adverse events								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
falling (plus one fell at conclusion of washout) The following 4 continuous scales were also used to assess for adverse effects of gabapentin (fatigue and decreased concentration) – all were very similar at baseline Digit span digit symbol fatigue impact scale adjective generation technique	1/21 14(5) 33(20) 57(39) 971(361)	0/21 14(4) 32(19) 65(41) 971(320)						
EDSS	No significant difference reported, but no data given.							

D.9 Botulinum toxin versus placebo

Table 36: HYMAN2000

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
HYMAN2000	RCT	N=74 Placebo n=16 500 u n=21 1000 u n=20 1500 u n=17	Inclusion: Adults with definite or probable MS and with disabling spasticity of the hip abductor muscles (Kurtzke EDS score ≥ 7) which had been stable for at least 6 mths before entry, and which caused moderate pain or difficulty in nursing (hygiene score ≥ 2) Exclusion: Acute exacerbations of MS, established contracture of the hip. Recent history of botulinum toxin, phenol injection, intrathecal baclofen use Age range 46.8 to 50.7 Females % range 9 to 16% Duration of MS range yrs 16.6 to 22.9 Concomitant medication skeletal muscle relaxant 9 to	Botulinum toxin Dysport 500, 1000, 1500 units Oral antispastic and analgesic medication was kept stable	Placebo	12 weeks but results presented for week 4 (in paper)	Modified Ashworth Score Muscle tone Spasm frequency Clinical global rating Upper leg pain Overall opinion Outcomes not extracted: Maximum distance between knees Passive hip abduction Hygiene assessment	Ipsen Ltd

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			17% analgesics 2 to 7% diazepam 4 to 7%					

Results: Most results not amenable to rev man because of the poor baseline equivalence, and lack of variance for continuous measures.

	Placebo n=16	500 u n=20	1000 u n=21	1500 u n=17		
Modified Ashworth score median Week 0 Week 4	 12.0 8.0	 8.5 4.0	 16.0 12.0	 14.0 8.0		
Muscle tone Patients with maximum score at Week 0 Week 4	 14 13	 17 13	 18 13	 15 10		
Spasm freq Patients with maximum score at week 0 Week 4	 7 3	 9 3	 13 7	 8 4		
Clinical global rating Median Week 0 Week 4	 3.0 2.0	 3.0 2.0	 3.0 2.0	 3.0 2.0		
Upper leg pain Pain free at week 0 Week 4	 3 10	 11 11	 6 7	 7 11		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Overall opinions Investigator positive response n Patient positive response		7 7	14 13	9 10	6 8			
Top 5		All disport patients	placebo	Proportion of patients reporting each AE				
Total adverse events		92	35					
Hypertonia		22	25					
Muscle weakness		14	6					
Fatigue		7	13					
Urinary tract infections		5	19					
Headache		5	13					

Table 37: GUSEV2008

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Efficacy and safety of botulinum type A toxin in adductor spasticity due to multiple sclerosis. Journal of musculoskeletal pain 2008; 16: 175-188	Multinational randomised double blind placebo controlled trial. Computer randomisation and clear allocation concealment. No mention of assessor blinding but likely given that the randomisation code was kept secure throughout the study.	106. 51 placebo and 55 BoNT-A. 1 withdrew, from BoNT-A group, after one study medication on day 1 (no reasons given).	Inclusion: ≥ 18 years old; definite or probable MS; disabling leg adductor muscle spasticity of both legs needing treatment. Exclusion: Severe fixed contractures of the hip, leg adductor spasticity not due to MS; scheduled to receive other investigational therapies; acute unstable MS; previous surgery on affected muscles; previous treatment with botulinum toxin in past 12 weeks; known sensitivity to botulinum toxin; previous phenol/alcohol to treat leg spasticity; meds affecting neuromuscular transmission; pregnancy, lactation or inadequate contraceptive measures. Baseline:	Botulinum type A toxin 1000-1500 Ipsen units injected into the adductor muscles of each leg (500-757 Ipsen units per leg). 35/55 received less than the maximum daily dose of 1500 Ipsen units	Placebo, as for intervention. 31/51 received less than the maximum injection volume of 7.5ml daily dose (equivalent volume to 1500 Ipsen units).	4 weeks	patient selected functional outcome (showing an improvement of at least 1 grade from baseline)	Not stated

	BoNT-A	Placebo
age	46.6	45.4

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Female	64%	67%					
			family Hx of MS	9.1%	11.8%					
			Duration of MS	12.9yrs	13.9yrs					
			Patients taking concomitant treatments	64%	75%					
			Right adductor tone 3 or more	40/55	32/51					
			Left adductor tone 3 or more	41/55	33/51					
			Moderate or severe upper leg pain (R)	28/55	26/51					

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Moderate or severe upper leg pain (L)	31/55	26/51					
			Great deal of difficulty performing a chosen function (mostly dressing but some chose maintenance of perineal hygiene and some chose transfer to toilet, as well as others).	22/55	20/51					
Results										

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			BoNT-A	**Placebo**				
Improvement of at least one grade in a chosen functional outcome – week 4			16/55	15/51				
Improvement of at least one grade in a chosen functional outcome – week 8			16/55	14/51				
Improvement of at least one grade in a chosen functional outcome – week 12			14/55	12/51				
Improvement of at least one grade in “maintenance of perineal hygiene”			20/50	11/46				
Improvement in Modified Ashworth scale			Data given in low resolution graph, but overall result: “At week 8 the difference in the proportion of patients who had an improvement of $\geq$ 1 point on the MAS for leg adductor muscle tone approached significance (0.067)”. No significant differences were reported for 4 and 12 weeks.					
Reduction of upper leg pain (R or L)			R leg: “a significant reduction in pain was seen in the right leg at weeks 8 and 12 in patients given BoNT-A compared with the placebo group [P=0.008 and P=0.013 respectively”.					

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures		Source of funding
			L leg: “a significant reduction in pain at weeks 4,8 and 12 in patients treated with BoNT-A compared with those given placeno [P=0.027, P=0.008, and P=0.008, respectively].							
Adverse events - any			29/55	14/51						
Adverse events – asthenia (most common AE)			12/55	3/51						

D.10 Intrathecal baclofen versus placebo

Table 38: MIDDEL1997

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Middel et al. Effect of intrathecal baclofen delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity. Journal of Neurology, Neurosurgery, and Psychiatry 1997; 63: 204-209	RCT. The RCT (intrathecal baclofen vs. placebo lasted 13 weeks, although there was an open non-RCT after that (which is not reported in this review). Method of randomisation not given, although it was stratified for some potential confounders (age,	22. No drop-outs or loss to follow up.	Patients with severe spasticity caused by multiple sclerosis or spinal cord injury. Mean (sd) age 48.3(12.7); 55% women; 59% MS. Inclusion: >18 years; chronic disabling spasticity of spinal origin inhibiting activities of daily living; insufficient response to oral baclofen, tizanidine or dantrolene medication. Exclusion: pregnancy; allergy to baclofen; no supraspinal symptoms Prior to the RCT all included patients were given ever-increasing test doses of baclofen and placebo 950, 75, 100 and 150micrograms) via intrathecal bolus injections to evaluate	Baclofen pump started telemetrically after implantation. Initial pump velocity based on response during test phase. For example, if response had been satisfactory at 75 micrograms of baclofen, pump velocity was adjusted to give a daily dosage twice that amount (ie 150micrograms/day or 6.25 micrograms/hour). If the response was not satisfactory, the	As for intervention, but saline placebo given instead, PLUS oral medication was maintained.	13 weeks	Ashworth scale Spasm score Self-reported pain Sickness impact profile (SIP) Hopkins symptom check list (HSCL)	Dutch sick-fund council. Thus no conflict of interest.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td>aetiology and sex). No report of allocation concealment. Blinding of both patient and clinician for RCT phase. Assessor blinding unclear.</td><td></td><td>response. All patients responded to one of the doses of baclofen.

Groups well balanced for age and sex, but aetiology different – 7/10 had MS in baclofen group and 6/12 had MS in placebo group. Group differences for some outcome variables at baseline: spasm score, Ashworth scale and self-reported pain score, but similar for SIP and HSCL overall scores.

<table><tr><td></td><td>Baclofen mean(sd)</td><td>Placebo mean(sd)</td></tr><tr><td>Age</td><td>45.8</td><td>46.3</td></tr><tr><td>%men</td><td>41.7%</td><td>50%</td></tr><tr><td>%MS</td><td>70%</td><td>50%</td></tr><tr><td>Spasm score</td><td>2.23(0.54)</td><td>1.83(0.66)</td></tr><tr><td>Ashworth score</td><td>2.51(0.70)</td><td>3.07(0.41)</td></tr></table></td><td>velocity of the pump was increased by 10%. A maximum of 2 dose increases was made during the 13 weeks treatment period.

Unclear if a placebo oral medication was given (see comparison column). If not given this would surely lead to unblinding, at least on the part of the clinician.</td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Self-reported pain score	4.20(2.98)	6.00(3.07)					
			SIP overall	31.72(9.8)	30.12(10.64)					
			HSCL overall	30.0(12.5)	31.0(21.6)					

Results: Because of group differences at baseline, the analysis was adjusted for this, using Cohen effect sizes.

	Baclofen (n=10)	Placebo (n=12)	Cohen effect sizes, estimating the group difference in the magnitude of the change between baseline and 3 months	U Wilcoxon p value		
spasm at 3 months (lower better)	1.65(1.1)	1.81(0.76)	0.2 (weakly favours baclofen)	<0.05		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ashworth scale at 3 months (lower better)	1.51(1.2)	2.87(0.57)	1.40 (strongly favours baclofen)	<0.01				
Self-reported pain score at 3 months (lower better)	2.75(3.22)	5.94(3.57)	0.94 (strongly favours baclofen)	<0.05				
Overall SIP at 3 months (lower better)	27.79(5.32)	28.98(8.83)	No effect size given	NS				
Overall HSCL at 3 months (lower better)	20.67(11.78)	28.22(18.43)	No effect size given	NS				

Table 39: LOUBSER1991

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Loubser et al. Continuous infusion of intrathecal baclofen: long-term effects on spasticity in spinal cord injury. Paraplegia 1991; 29: 48-64	Modified cross-over trial. Patients had 10 intervals of intrathecal drug infusion over 5 days (intervals of 12 hours). One of these intervals was of saline placebo and 9 were of baclofen. The order was randomised and the assessor was blinded. It is unknown if the patient and health care professionals	9.	Patients with traumatic non-progressive spinal cord injury. Spasticity refractory to conventional therapy, including oral baclofen. Patients were weaned off all spasticity medications, and so were kept as inpatients for observation. Mean age 45.6 (range 22-63).	9 intervals of 12 hours of intrathecal baclofen. Doses were modified in each interval based on response. Individual doses were a mean 163.9 micrograms, range 50-400.	1 interval of 12 hours of saline placebo	5 days	Ashworth scale (higher worse) Mean reflex score (higher worse; scale of 0-6 where 0=no response and 6=sustained clonus, averaged over both knees and ankles)	National Institute on Disability and Rehabilitation research, grant (ie no conflict of interest)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	were blinded, though the use of a placebo makes this probable. The major problem with the methodology was that the best result in the 9 baclofen intervals (probably corresponding to the best dose) was used versus that in the single placebo interval. This will have created bias arising from the removal							

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	of poor baclofen results arising by chance but not poor placebo results arising by chance. There was a further longitudinal phase but this is not reported here.							
Results								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Mean paired difference (sd of differences) placebo – baclofen [not given directly in paper but calculated from raw data provided]	**Mantel Haenszel paired analysis for categorical data - RR for improvement* in baclofen relative to placebo, taking into account cases where paired outcomes are the same [not given directly in paper but calculated from raw data provided]**						
Ashworth score	1.37(0.69)	RR: 1.5 lnRR (SE): 0.405 (0.236)						
Reflex score	1.92 (1.56)	RR: 1.286 lnRR (SE): 0.251 (0.178)						
Adverse events	Reported, but not clear what group patients were in when adverse events experienced.							
* It was not possible to analyse worsening/the same as this led to infinities in the calculation (x/0).								

Table 40: MEYTHALER ET AL.2001

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Meythaler et al. Intrathecal baclofen for spastic hypertonia from stroke. Stroke 2001; 32: 2099-2109	RCT. No details of randomisation or allocation concealment. Patients and raters blinded. No mention of blinding of health care professionals.	22.	CVA patients with intractable spastic hypertonia >6 months out from onset of CVA. Spasticity interfered with sleep and activities of daily living. Patients resistant to other therapies including oral baclofen. Inclusion: >16 years; severe chronic spastic hypertonia of legs (arms could be affected as well) of at least 6 months duration characterised by an Ashworth score of at least 3 in one affected extremity or an average spasm score of at least 2 in the affected limbs on the day of screening; resistant to other treatments Baseline equivalence for: leg and arm Ashworth scale, reflex score and spasm score.	Bolus injection of baclofen (50 micrograms) to intrathecal space (L3-4 or L2-3) via lumbar puncture and 1 cc injected. Thus this is not strictly intrathecal baclofen. Another (unblinded) higher dose (75 or 100 micrograms) bolus was offered to those not fully responding to the first bolus but the results of that are not included here.	Bolus injection of placebo to intrathecal space (L3-4 or L2-3) via lumbar puncture and 1 cc injected.	6 hours	Ashworth scale (higher worse) Spasm score (higher worse; 0=no spasms and 4=spasms occurring >10/h) Deep tendon reflex score (higher worse; 0=no reflexes to 5=clonus)	Medtronic. Thus very likely conflict of interest.
Results:								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Most data given in low resolution graphs, but some text details given for effect directions and effect sizes.								
	Baclofen bolus	**Placebo bolus**						
Ashworth in lower extremities	Decreased from 3.3 (1.2) to 1.4 (0.7) 6 hours after a baclofen bolus	No data in text, but stated that there were significant differences between baclofen and placebo at 6 hours ($p<0.0001$, Wilcoxon signed ranks test)						
Spasm in lower extremities	Decreased from 1.2(1.2) to 0.1 (0.3) 6 hours after a baclofen bolus	No data in text, but stated that there were significant differences between baclofen and placebo at 6 hours ($p<0.0077$, Wilcoxon signed ranks test)						
Reflex score in lower extremities	Decreased from 2.1(1.2) to 0.1 (0.5) 6 hours after a baclofen bolus	No data in text, but stated that there were significant differences						

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			between baclofen and placebo at 6 hours (p<0.0001, Wilcoxon signed ranks test)					
Ashworth in upper extremities		Decreased from 2.8 (1.1) to 1.8 (0.8) 6 hours after a baclofen bolus	No data in text, but stated that there were significant differences between baclofen and placebo at 6 hours (p<0.0001, Wilcoxon signed ranks test)					
Spasm in upper extremities		Decreased from 0.7(1.0) to 0.2 (0.4) 6 hours after a baclofen bolus	No data in text, but stated that there were significant differences between baclofen and placebo at 6 hours (p<0.0177, Wilcoxon signed ranks test)					
Reflex score in upper extremities		Decreased from 2.1(0.9) to 1.2 (0.9) 6	No data in text, but stated that there were significant					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	hours after a baclofen bolus		differences between baclofen and placebo at 6 hours (p<0.0006, Wilcoxon signed ranks test)					

Table 41: HUGENHOLTZ1992

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hugenholtz et al. Intrathecal baclofen for intractable spinal spasticity – a double-blind cross-over comparison with placebo in 6	Randomised double cross-over trial, with 48 hour wash-out. Patients and assessors blinded to the treatment. No mention of whether HCPs blinded but it	6.	Inclusion: Age 16-60; spasticity secondary to SCI or MS; reversible spasticity mainly in legs and trunk; community independent and ambulatory at least by wheelchair; failure of optimum pharmacotherapy and physiotherapy; no systemic disorders that	Lumbar sub-arachnoid catheter and access port implanted in OR. Optimum dose for all subjects decided by prior test bolus injections over a period of days. Optimum dose was that just below the dose that diminished leg and trunk spasms and started to cause upper limb weakness.	See intervention column	24 hours	Modified Ashworth (0-5; 5 worst) Spasm score (0-4; 4 worst) Reflex score (0-4; 4 worst) Disability (questionnaire)	PSI foundation and CIBA-GEIGY Canada ltd (therefore potential conflict of interest).

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
patients. The Canadian Journal of Neurological Sciences 1992; 19:188-195	appears as though the hospital pharmacy was responsible for adjusting doses and medications so HCP		could exacerbate spasticity; normal CSF flow; no previous ablative therapy to spinal cord, roots, peripheral nerves or muscles; no prior tenotomise/joint fusions; no allergy to baclofen.	Cross over phase took place over 11 days. Subjects randomised to either: 1. Intrathecal baclofen on days 2 and 8 and intrathecal placebo (saline) on days 5 and 11 2. Intrathecal placebo on days 2 and 8 and				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	blinding likely.			intrathecal baclofen (saline) on days 5 and 11. Treatments lasted 24 hours. Thus treatments separated by 48 hour washout. Concentration adjusted so that individual dose (in one or two daily injections) delivered in volume of 1-2.5ml. Daily doses ranged from 22.5 micrograms to 125 micrograms. Only the 22.5microgram dose was given in 2 bolus injections.				
Results: Very poorly described. The 2 baclofen round results were averaged and the 2 placebo round results were averaged. The data below were extracted from the text and tables in the paper. We know that there were only zeroes in the placebo only arm as the paper stated that the reported placebo treatment effects “were only observed in subjects who also demonstrated baclofen treatment effects”. Mantel-Haenszel RRs for paired categorical outcomes were calculated by the author of this review (not used in the paper itself).								

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Test parameter	Number with an improvement from baseline in both placebo and intrathecal baclofen	Number with an improvement from baseline in intrathecal baclofen only	Number with an improvement from baseline in placebo only	RR	ln RR	SE (ln RR)
Disability (questionnaire)	2	3	0	2.500	**0.916**	**0.548**
Spasm score in arms	0	0	0	-	**-**	**-**
Spasm score in legs	2	4	0	3.000	**1.099**	**0.577**
Ashworth (tone) in arms	1	0	0	1.000	**0.000**	**0.000**
Ashworth (tone) in legs	4	2	0	1.500	**0.405**	**0.289**
Reflexes in arms	0	1	0	-	**-**	**-**
Reflexes in legs	1	3	0	4.000	**1.386**	**0.866**

Table 42: ORDIA1996

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ordia et al. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. J Neurosurg 1996; 85: 452-457	Randomised double blind placebo controlled trial, as a screening phase prior to a open trial of intrathecal baclofen	9	Intractable spasticity of spinal cord origin; medical treatment had failed in all. More information available but for a larger group of which these 9 were a part.	Bolus injection of 50 micrograms baclofen to intrathecal space on days 1 and 2. Code then broken. If any baclofen patients had no response, then 75 micrograms baclofen to intrathecal space on days 3 and 4. Code then broken. If any baclofen patients had no response, then 100 micrograms	Bolus injection of 50 micrograms saline to intrathecal space. It is unclear, but it seems that the placebo group did not mirror the baclofen group in the sense that if a placebo participant	immediate	A reduction in the mean Ashworth score or the mean spasm frequency score of 2 or more points for at least 4 hours. Those who responded to placebo or did not respond to the 100 microgram bolus were considered non-responders.	None reported

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				baclofen to intrathecal space on days 5 and 6.	did not show improvement, 2 further opportunities were not given (as for baclofen). This creates bias, as the baclofen patients had 3 opportunities to improve compared to the placebo group. Hence chance effects were more likely in the			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
					baclofen group.			
Results: All responded positively to the bolus dose of baclofen and none responded to placebo. Numbers in each group not reported.								

Table 43: MEYTHALER ET AL.1996

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Meythaler et al. Prospective study on the iuse of bolus intrathecal baclofen for spastic hypertonia due to acquired brain injury. Arch Phys med Rehabil 1996; 77: 461-6	Randomised double-blind placebo-controlled cross-over study. Patient and investigator blinded.	11.	Brain injury patients aged 20-37; 9 men and 2 women; severe hypertonia interfering with ADL; 9 injured in motor vehicle accidents, one by a gunshot wound and one due to an anoxic episode. Inclusion: 18-65 years; severe chronic spastic hypertonia of legs (arms could be affected as well) of at least 12 months duration characterised by an Ashworth score of at least 3 in one affected extremity or an average spasm score of at least 2 in the affected limbs on the day of screening; resistant to other treatments; failure to respond to oral antispastic medications, or intolerant to them. Exclusion: Pregnancy; sensitivity to baclofen; impaired renal,	Bolus injection of baclofen (50 micrograms) to intrathecal space (L3-4 or L2-3) via lumbar puncture and 1 cc injected. Thus this is not strictly intrathecal baclofen. Cross-over occurred at least 48 hours after the initial administration.	Bolus injection of placebo to intrathecal space (L3-4 or L2-3) via lumbar puncture and 1 cc injected. Cross-over occurred at least 48 hours after the initial administration.	6 hours	Ashworth scale (higher worse) Spasm score (higher worse; 0=no spasms and 4=spasms occurring >10/h) Deep tendon reflex score (higher worse; 0=no reflexes to 5=clonus)	None reported.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			hepatic or gastrointestinal function. No baseline difference in leg or arm Ashworth, spasm or reflex scores.					

Results:

Most data given in low resolution graphs, but some text details given for effect directions and effect sizes.

	Baclofen bolus	Placebo bolus				
Ashworth in lower extremities	Decreased from 4.2 (0.8) to 2.2 (0.6) 4 hours after a baclofen bolus	No data in text, but stated that there were significant differences between baclofen and placebo (favouring baclofen) at 4 hours ($p<0.0084$) and 6 hours ($p<0.0163$, Wilcoxon signed ranks test)				
Spasm in lower extremities	Decreased from 3.1(1.0) to 1 (0.7)	No data in text, but stated that there were significant				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	4hours after a baclofen bolus		differences between baclofen and placebo at 4 hours (p<0.0073) and 6 hours (p<0.0049, Wilcoxon signed ranks test)					
Reflex score in lower extremities	Decreased from 3.3(0.5) to 1 (1.3) 4hours after a baclofen bolus		No data in text, but stated that there were significant differences between baclofen and placebo at 4 hours (p<0.0086) and 6 hours (p<0.0085, Wilcoxon signed ranks test)					
Ashworth in upper extremities	Decreased from 3.3 (1.3) to 1.9 (0.8) 4 hours after a baclofen bolus		No data in text, but stated that there were significant differences between baclofen and placebo at 4 hours (p<0.0097,					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Wilcoxon signed ranks test)					
Spasm in upper extremities	Decreased from 1.8(1.3) to 0.6 (1) 4 hours after a baclofen bolus		No data in text, but stated that there were significant differences between baclofen and placebo at 4 hours (p<0.0117, Wilcoxon signed ranks test)					
Reflex score in upper extremities	Decreased from 2.7(0.5) to 1.7 (0.6) 4 hours after a baclofen bolus		No data in text, but stated that there were significant differences between baclofen and placebo at 4 hours (p=0.0272, Wilcoxon signed ranks test)					

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Appendix E – Forest plots

E.1 Baclofen versus placebo

Figure 2: self-evaluation of gait improvement (higher better)

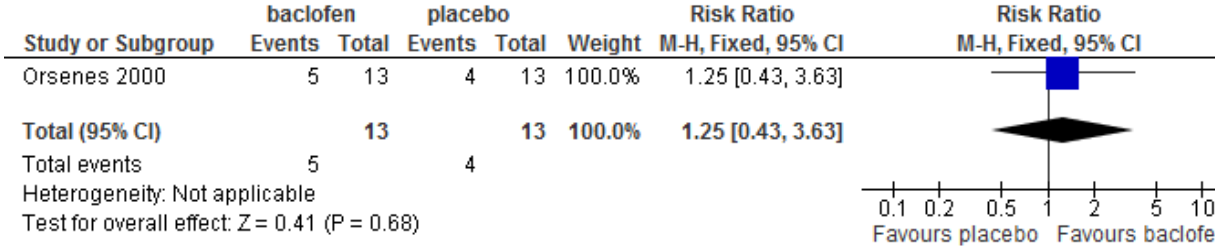


Figure 3: numbers showing improvement in Ashworth score

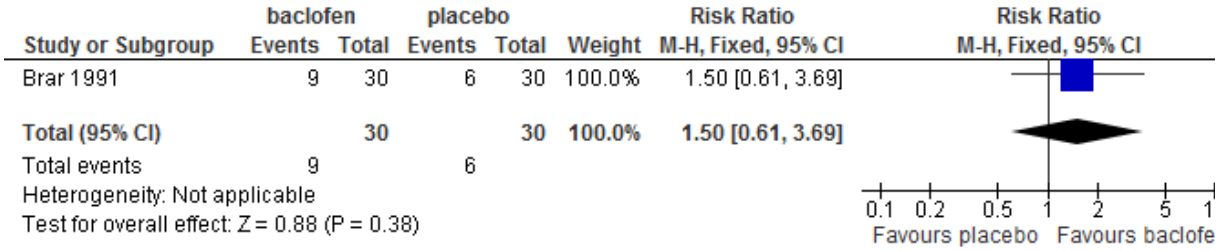


Figure 4: detectable improvement in spasticity assessed by investigators

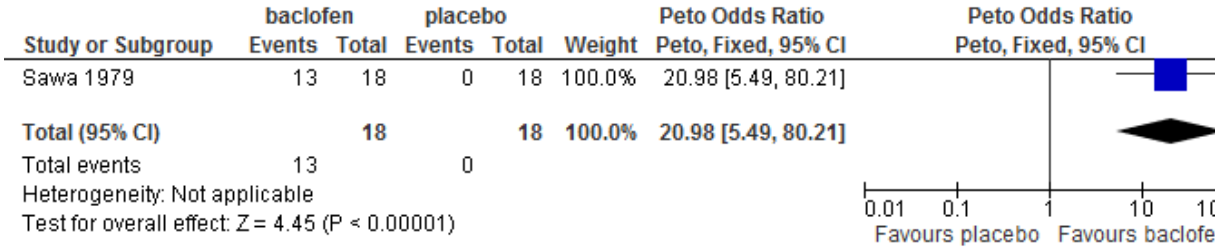
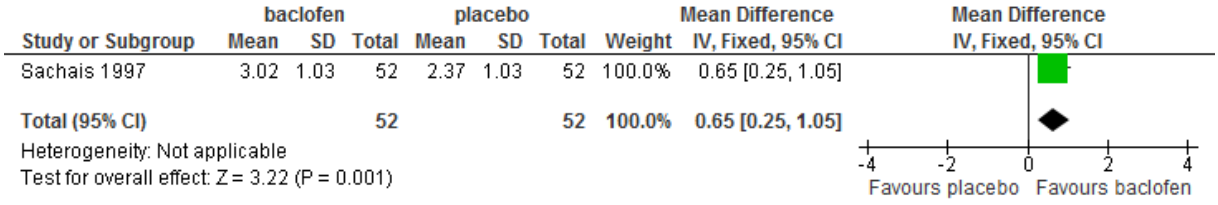


Figure 5: Physician assessment of clinical change in overall spastic state (higher better)



1

Figure 6: Physician assessment of clinical change in daytime spasms (higher better)

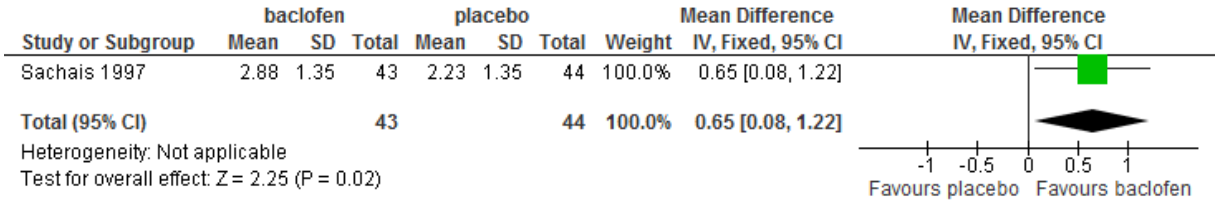


Figure 7: Physician assessment of clinical change in night-time spasms (higher better)

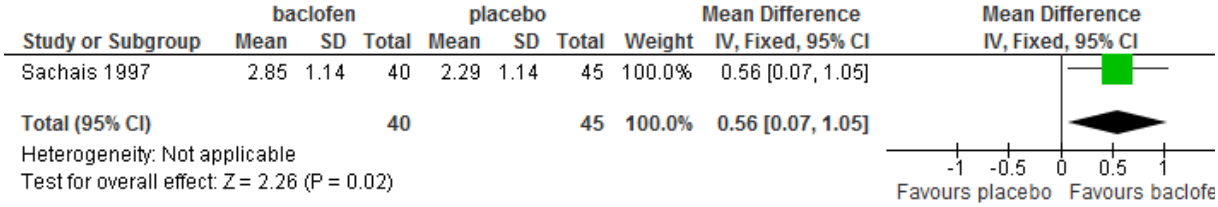
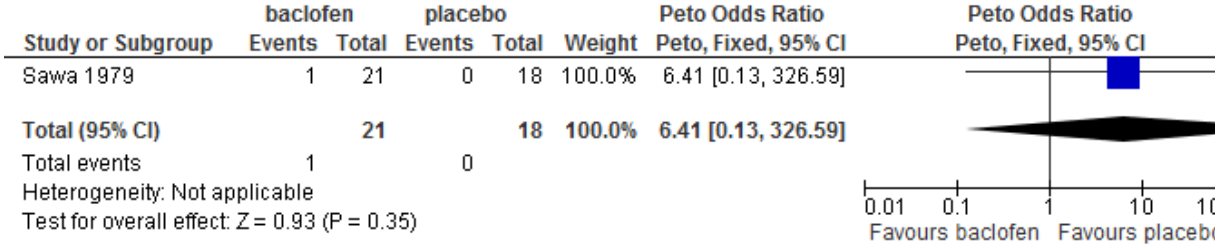


Figure 8: Adverse events leading to treatment withdrawal



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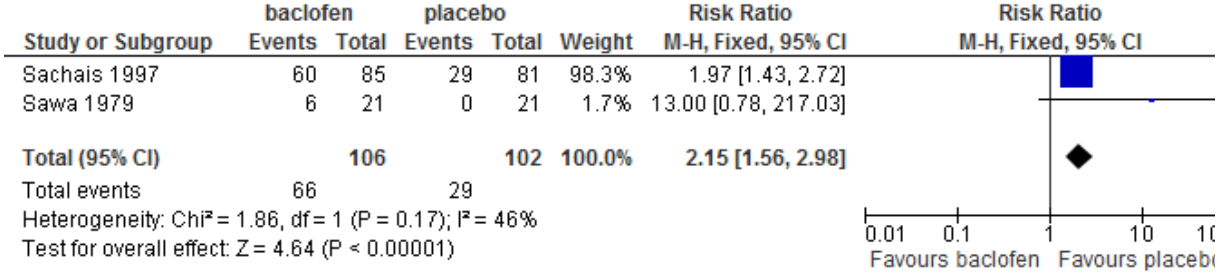
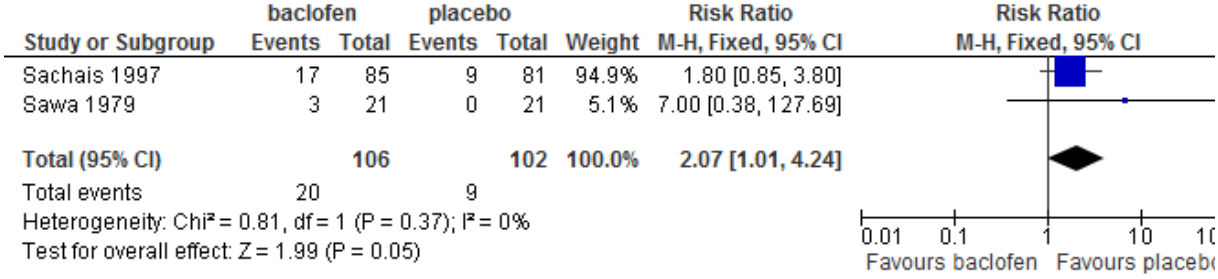
3

Figure 9: Adverse events - somnolence



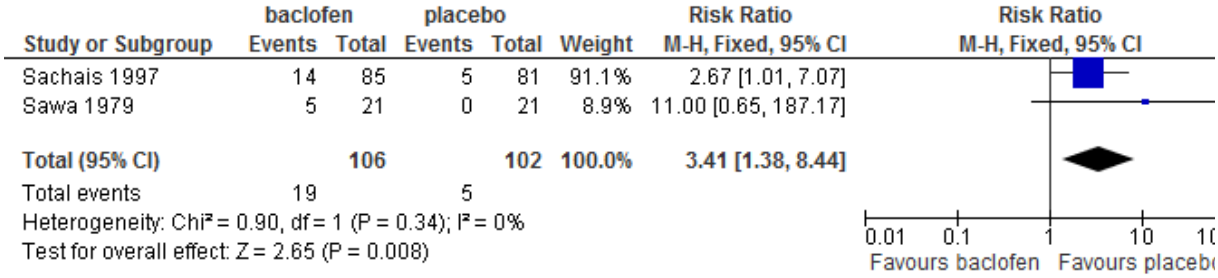
1

Figure 10: Adverse events - weakness



2

Figure 11: Adverse events - nausea

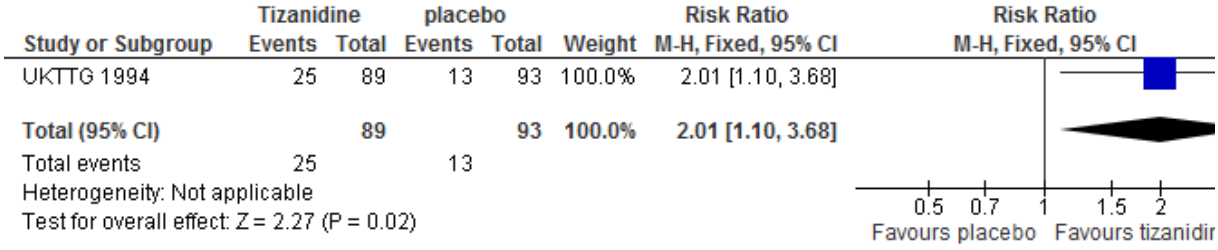


3

E.24 Tizanidine versus placebo

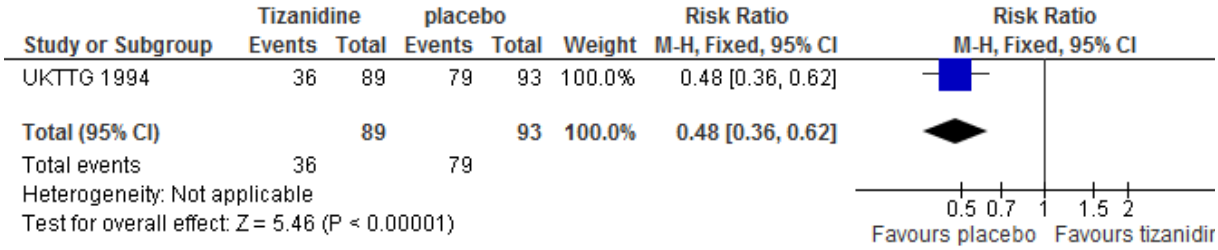
5

Figure 12: Patient assessment of efficacy – good or very good



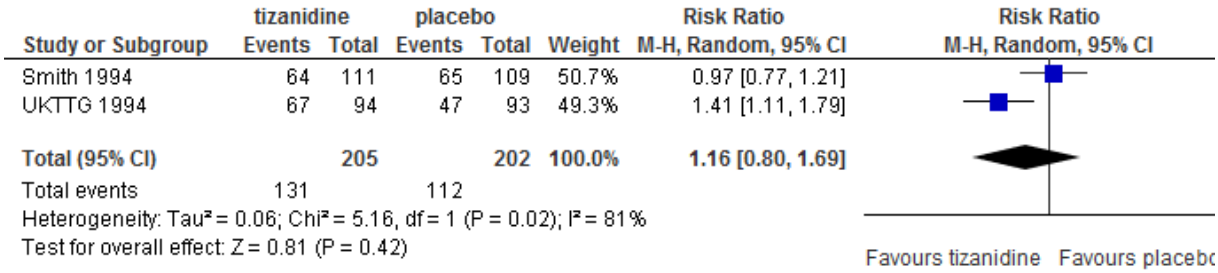
6

Figure 13: patient assessment of tolerability – good or very good



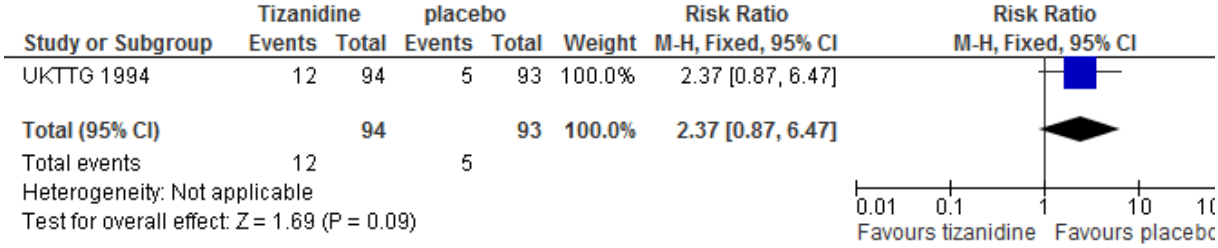
1

Figure 14: Ashworth score – improved



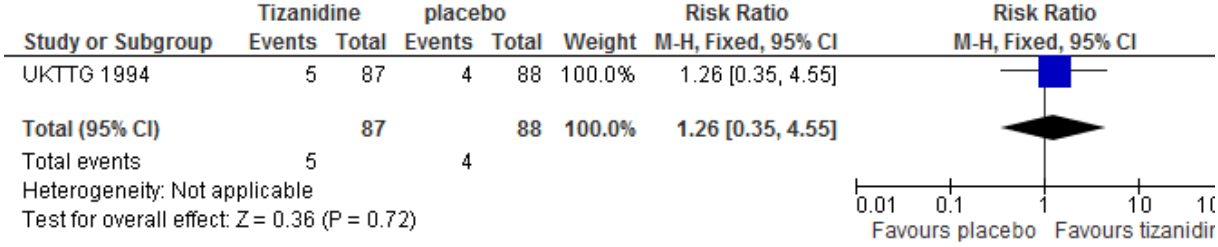
2

Figure 15: Patients discontinuing due to adverse events



3

Figure 16: Numbers with improved upper limb function (higher better)

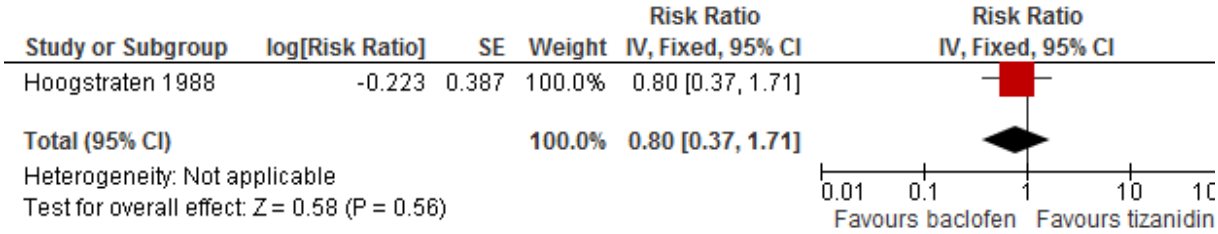


4

E.31 Tizanidine versus baclofen

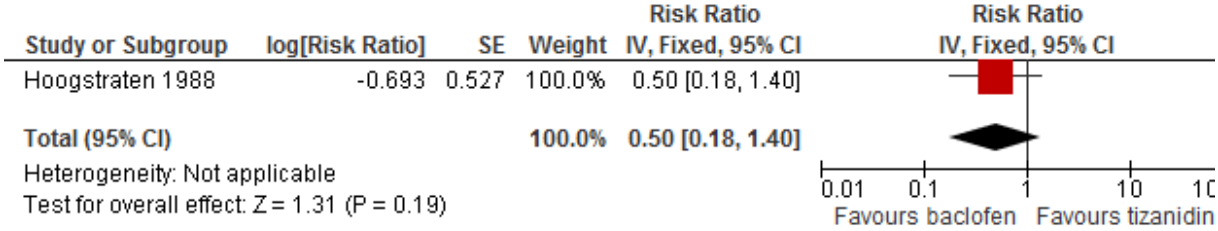
2

Figure 17: spasticity worse or no better



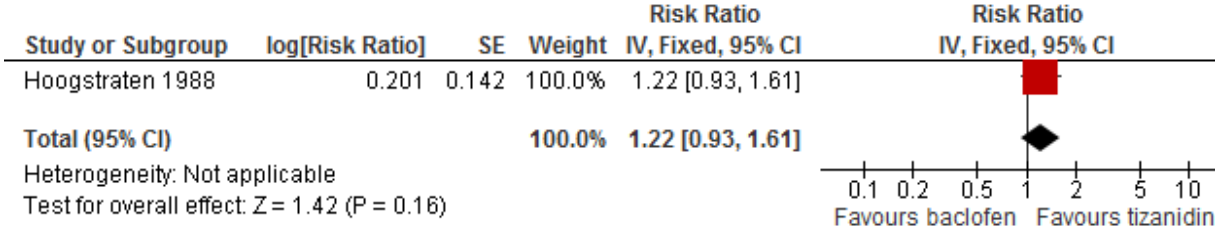
3

Figure 18: spasms worse or no better



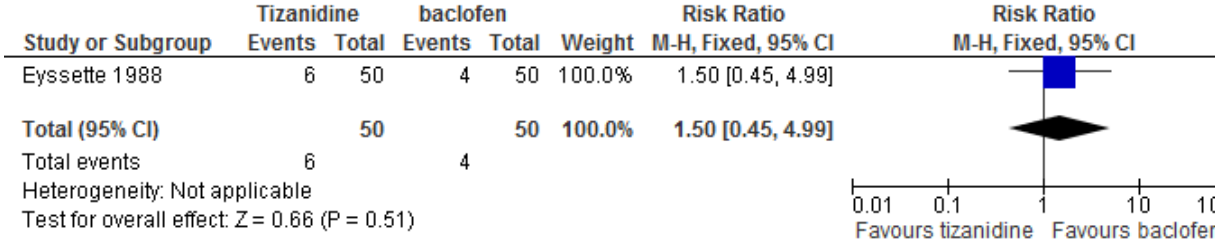
4

Figure 19: mobility worse or no better



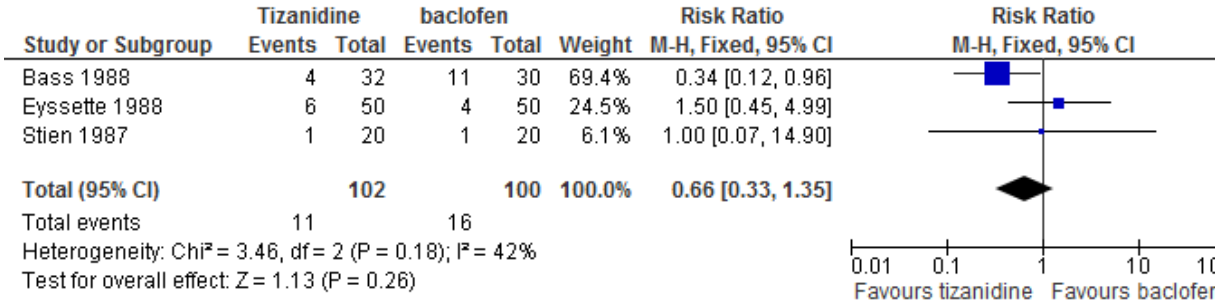
5

Figure 20: overall evaluation of tolerability – patients stating treatment was poorly tolerated



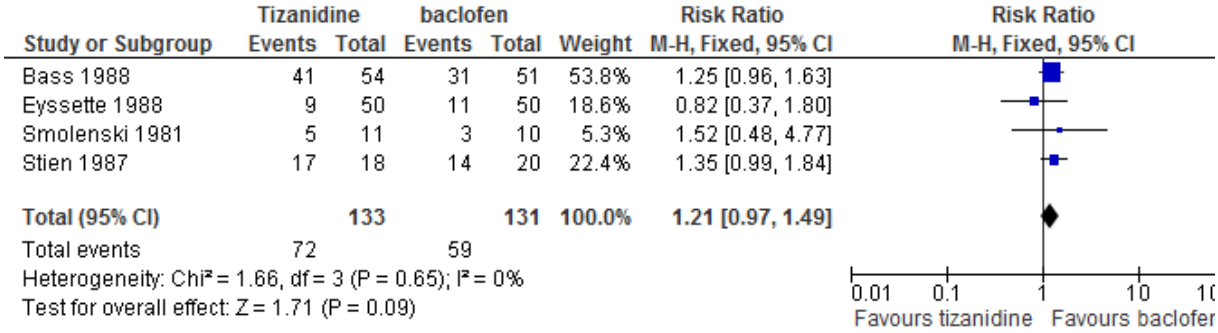
6

Figure 21: discontinuation due to adverse events



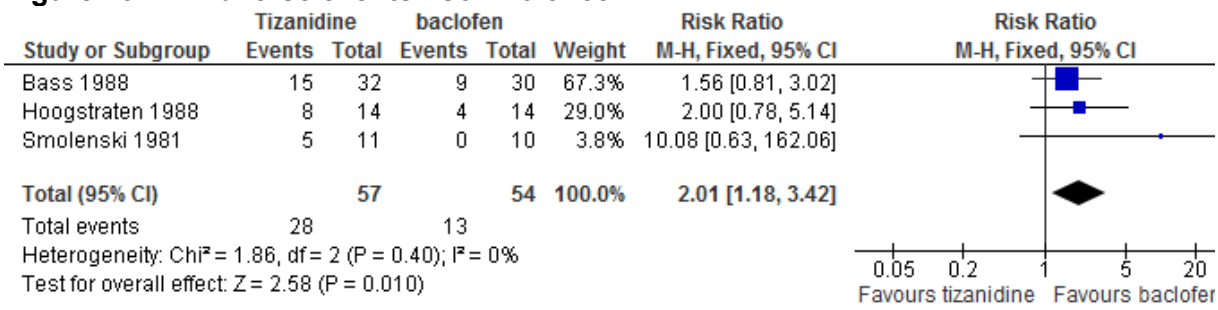
1

Figure 22: overall assessment of patient of the efficacy (moderate or poor)



2

Figure 23: Adverse events - somnolence



3

Figure 24: Adverse events - nausea

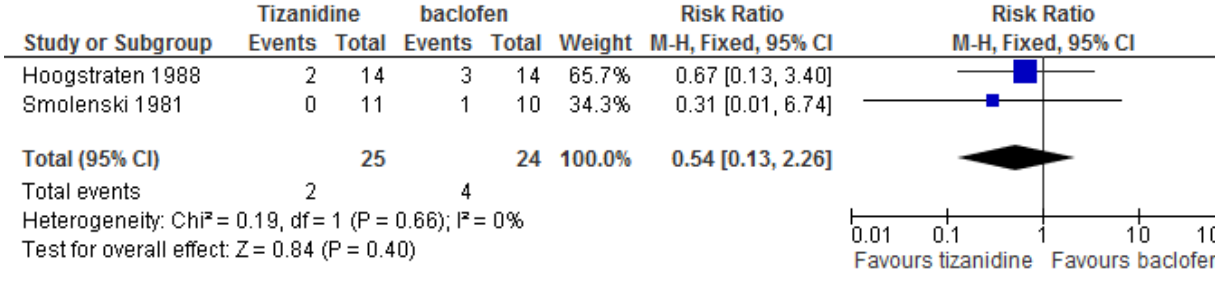
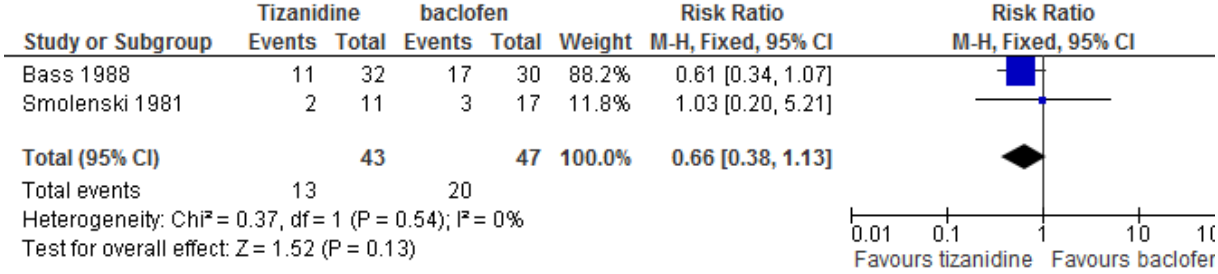


Figure 25: Adverse events - weakness



E.43 Diazepam versus baclofen

Figure 26: better patient rated global response

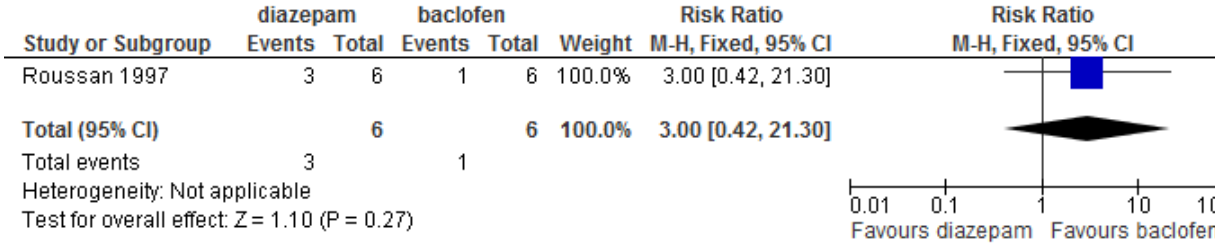


Figure 27: Adverse events - weakness

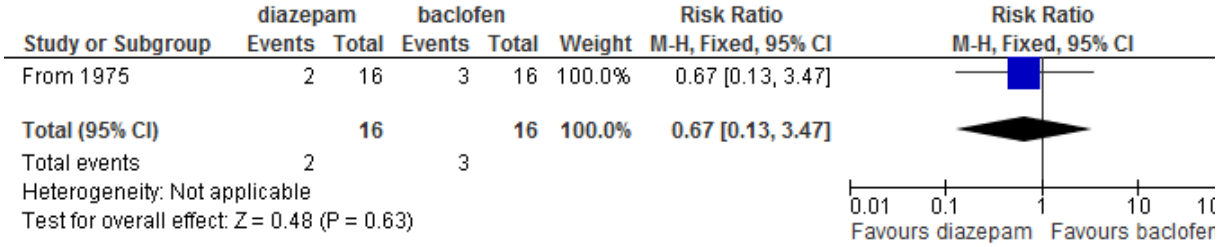
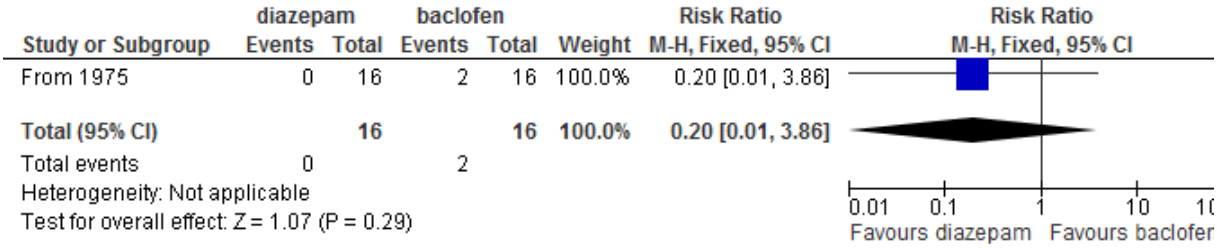
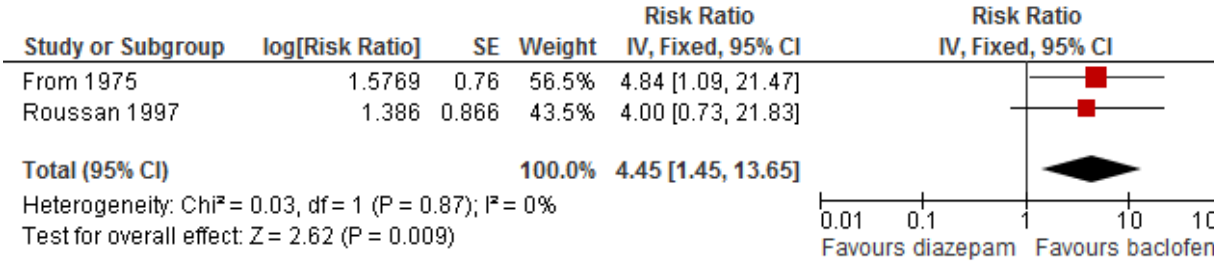


Figure 28: Adverse events - nausea



1

Figure 29: Adverse events - somnolence

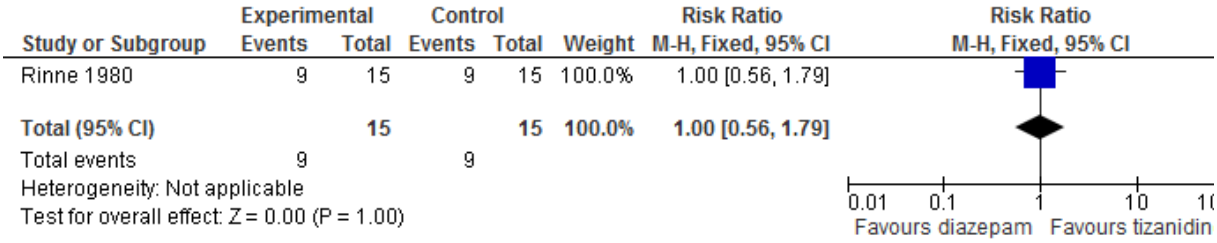


2

E.53 Tizanidine versus diazepam

4

Figure 30: Numbers with improvement in spasticity (higher better)

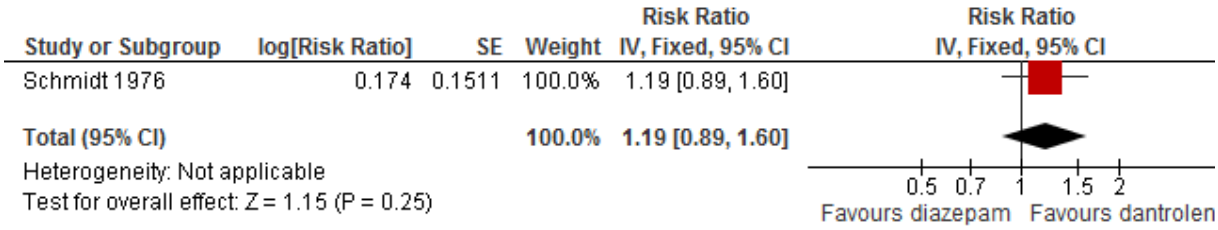


5

E.66 Dantrolene versus diazepam

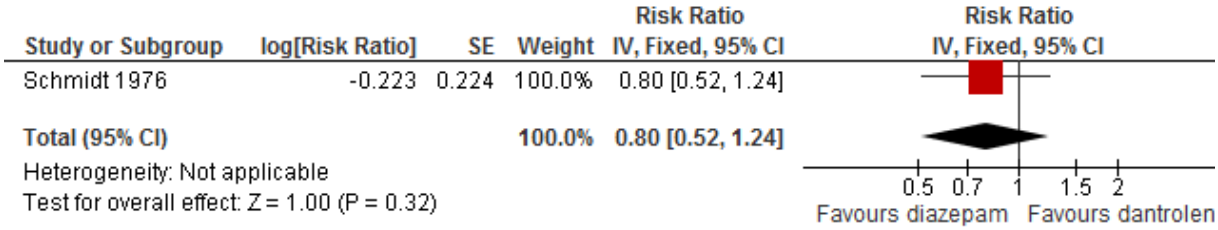
7

Figure 31: improvements in cramps or spasms over treatment



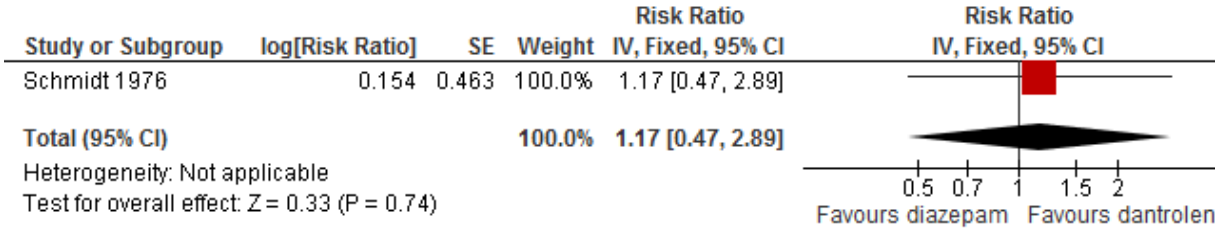
1

Figure 32: improvement in stiffness over treatment



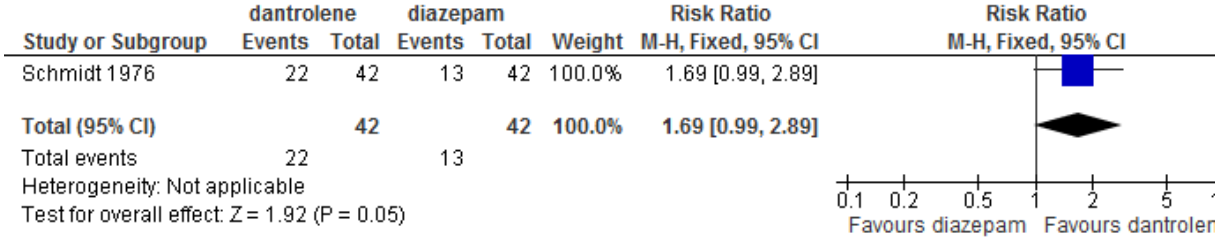
2

Figure 33: improvements in gait over treatment



3

Figure 34: drug preference (higher better)

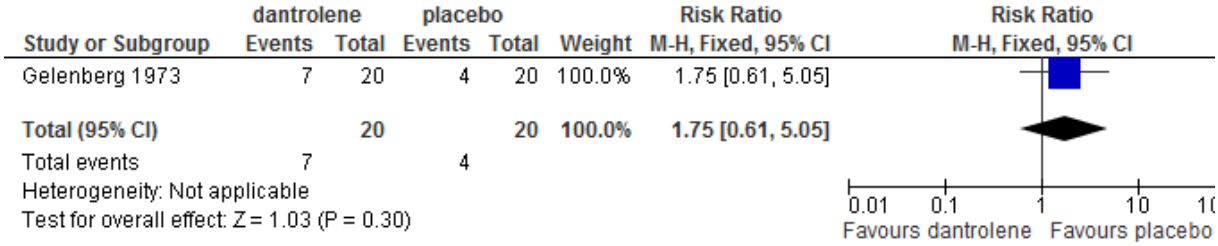


4

5

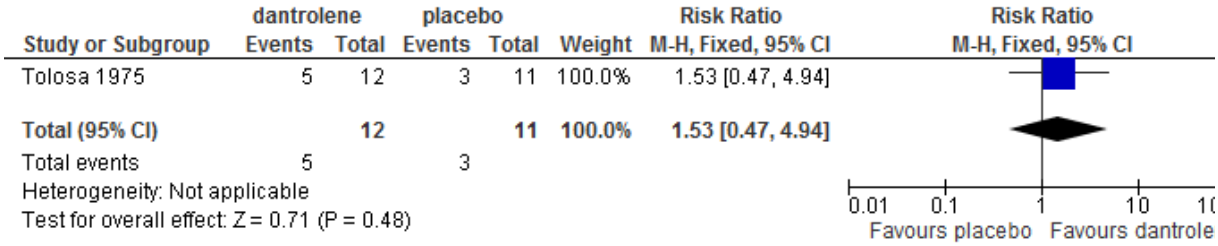
E.71 Dantrolene versus placebo

Figure 35: patient preference



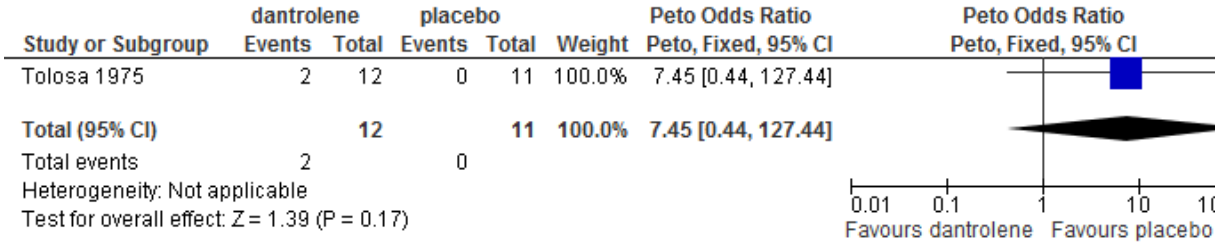
2

Figure 36: reduction in spasticity



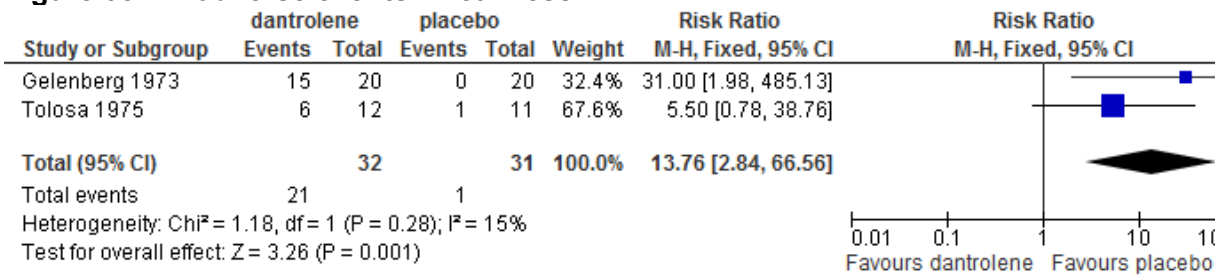
3

Figure 37: adverse events leading to treatment discontinuation



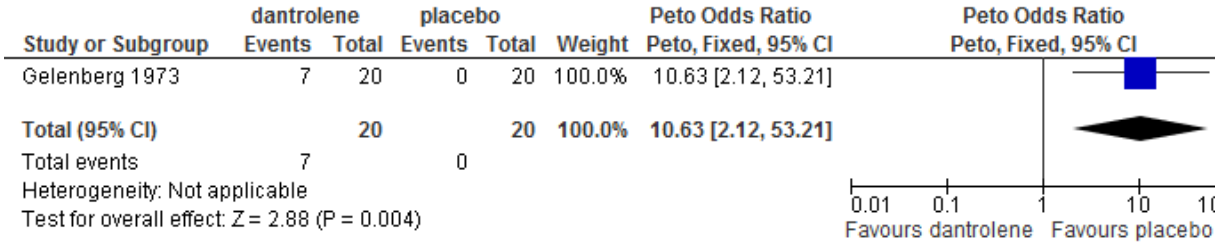
4

Figure 38: adverse events - weakness



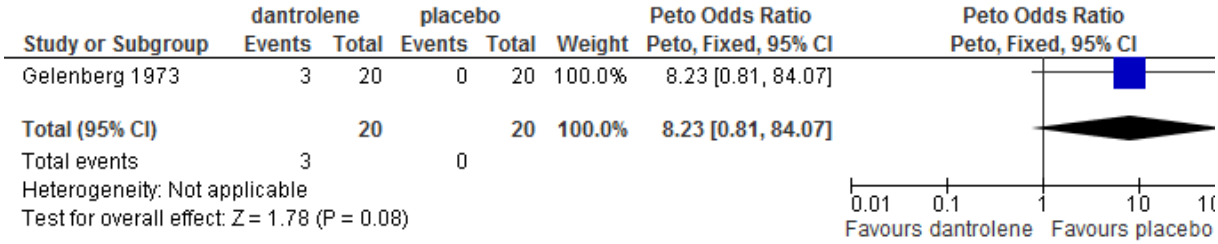
5

Figure 39: adverse events - nausea



1

Figure 40: adverse events - somnolence

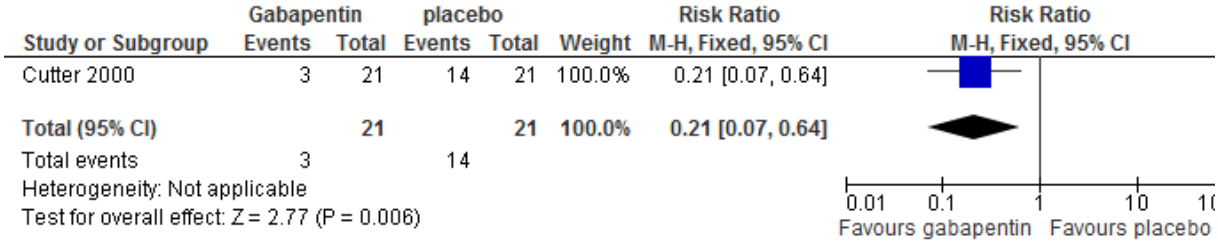


2

E.83 Gabapentin versus placebo

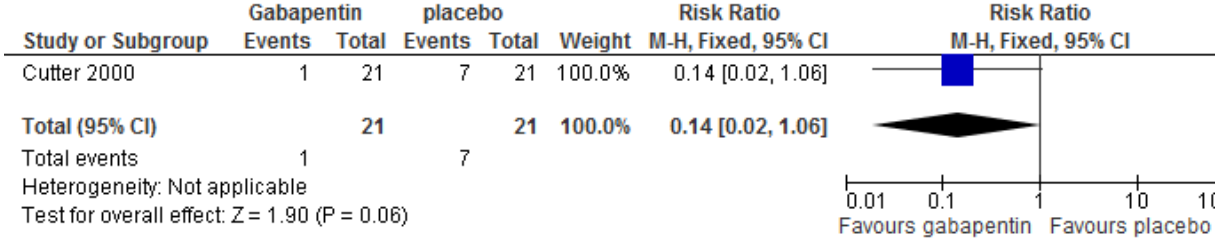
4

Figure 41: existence of moderate or severe spasms (lower better)



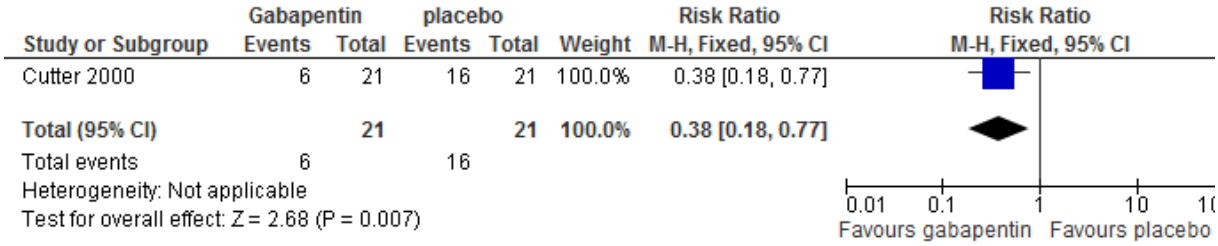
5

Figure 42: spasm frequency >1 time per hour at follow up (lower better)



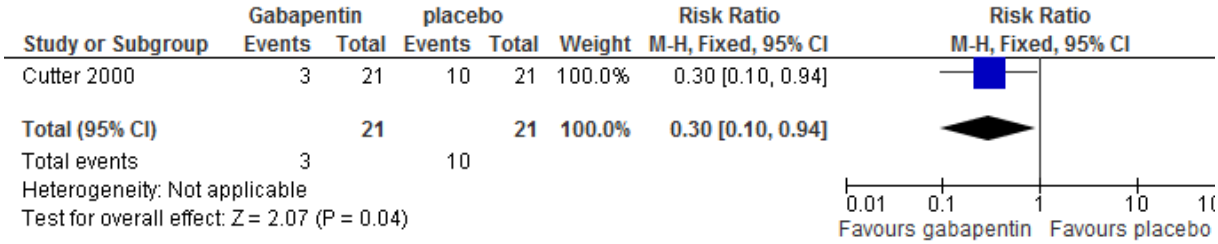
6

Figure 43: spasticity worse or unchanged (lower better)



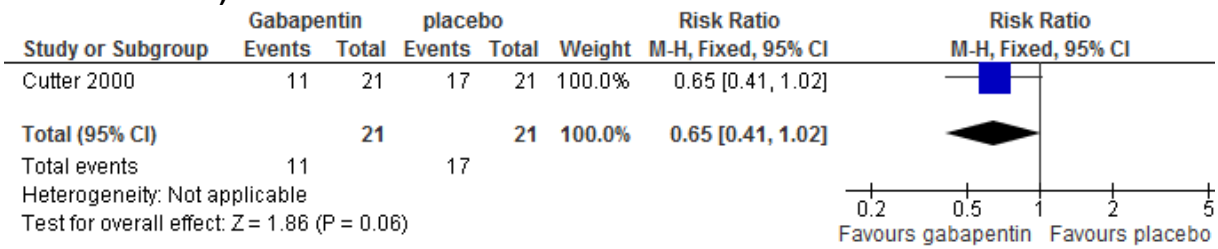
1

Figure 44: Modified Ashworth score >4 at follow up (lower better)



2

Figure 45: spasticity making function difficult or impossible at follow up (lower better)



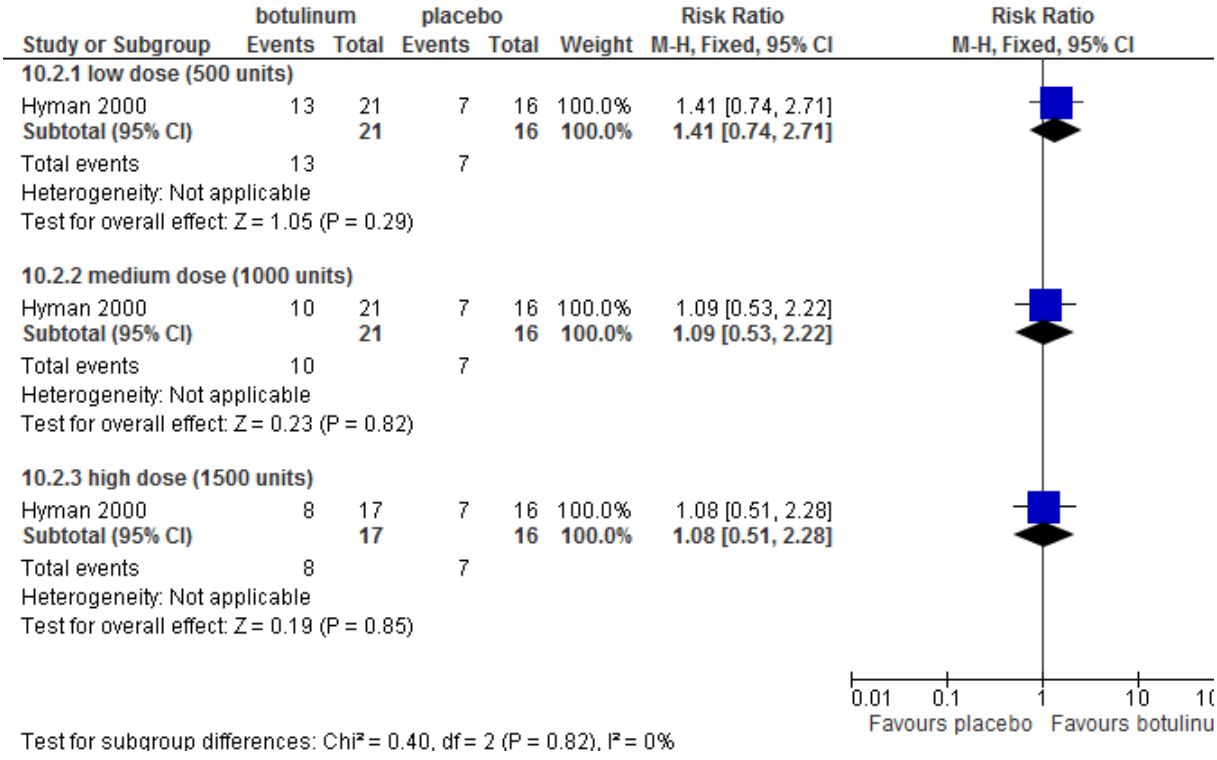
3

4

E.95 Botulinum versus placebo

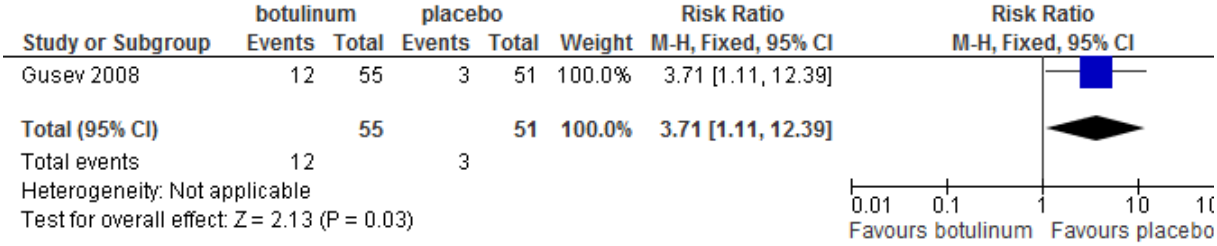
6

Figure 46: positive patient response



1

Figure 47: adverse events - weakness



2

E.10 3 Intrathecal baclofen versus placebo

4

5

Figure 48: Proportion with improvement in Ashworth scale

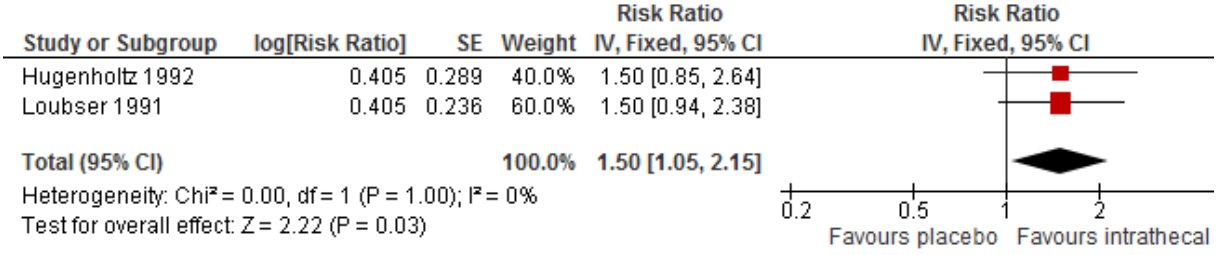
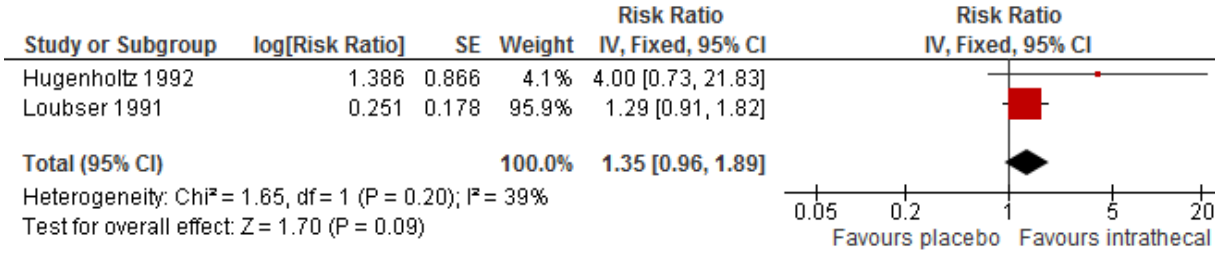
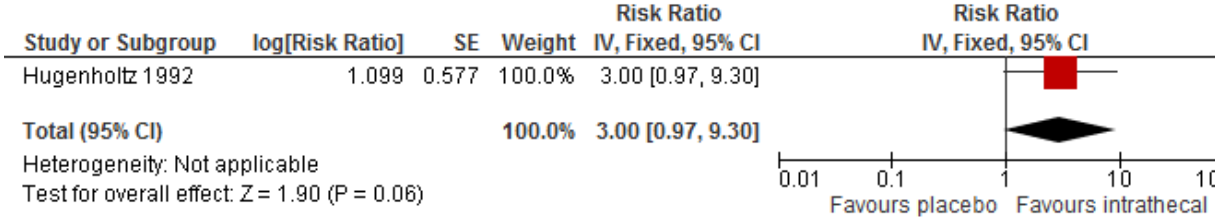


Figure 49: Proportion with improvement in reflex score



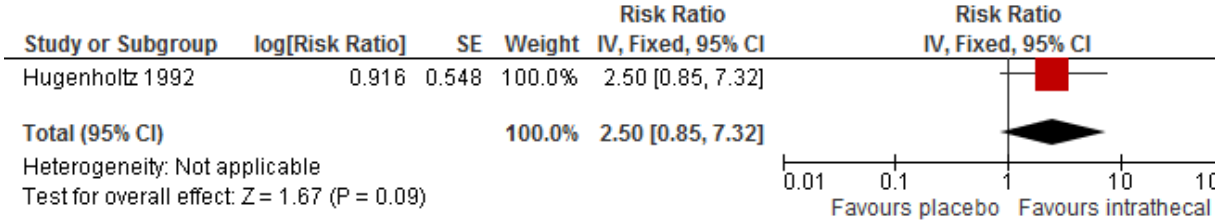
1

Figure 50: Proportion with improvement in spasm score



2

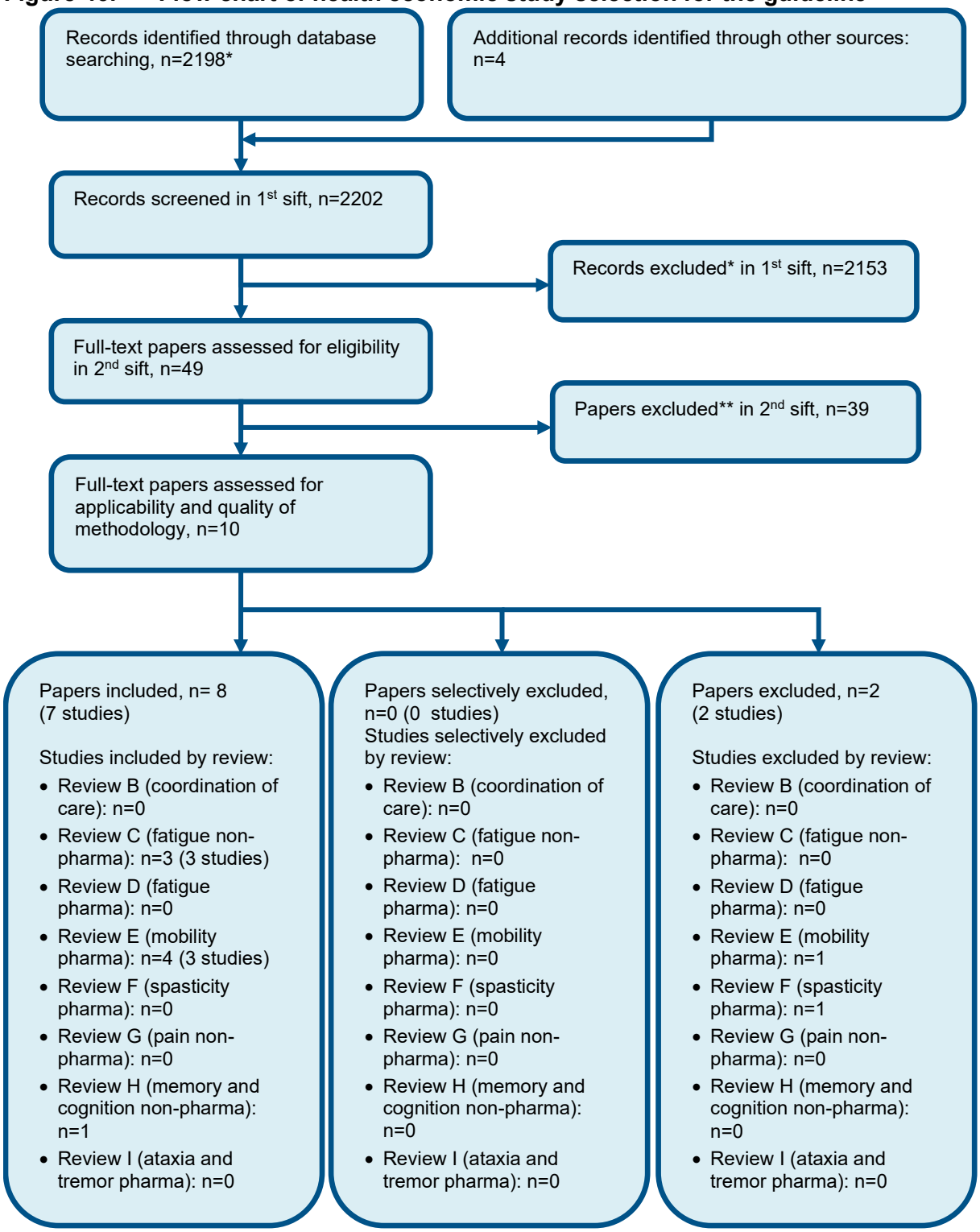
Figure 51: Proportion with improvement in disability (questionnaire)



3

Appendix F – Economic evidence study selection

Figure 46: Flow chart of health economic study selection for the guideline



* Excluding conference abstracts.
**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G – Economic evidence tables

None.

Appendix H – Health economic model

New cost-effectiveness analysis was not conducted in this area.

1 Appendix I – Excluded studies

2 Clinical studies

3 Table 444: Studies excluded from the clinical review

Study	Code [Reason]
(1997) Tizanidine for spasticity. Medical letter on drugs and therapeutics 39(1004): 62-63	- Conference abstract/trial registry record
(2010) Is it clinically effective to treat arm flexor spasticity, with Botulinum toxin – type A (BoNTA) and physiotherapy, as soon as signs of abnormal muscle activity are observed? (A phase II study).	- Conference abstract/trial registry record
Amjad, F., Pagan, F., Lax, A. et al. (2017) A comparison of muscular atrophy between botulinum toxin types A and B. Movement Disorders 32(supplement2): 756	- Conference abstract
Ammendolia, A., d'Esposito, O., Barletta, M. et al. (2018) Treatment of spasticity in multiple sclerosis: Botulinum toxin A injection versus radial shockwave therapy. Annals of Physical and Rehabilitation Medicine 61(supplement): e364-e365	- Comparator in study does not match that specified in this review protocol
Badillo, S.P.J. and Jamora, R.D.G. (2019) Zolpidem for the treatment of dystonia. Frontiers in Neurology 10(jul): 779	- Study does not contain an intervention relevant to this review protocol
Baker, Jennifer A and Pereira, Gavin (2013) The efficacy of Botulinum Toxin A for spasticity and pain in adults: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. Clinical rehabilitation 27(12): 1084-96	- Systematic review used as source of primary studies
Baker, Jennifer A and Pereira, Gavin (2016) The efficacy of Botulinum Toxin A for limb spasticity on improving activity restriction and quality of life: a systematic review and meta-analysis using the GRADE approach. Clinical rehabilitation 30(6): 549-58	- Systematic review used as source of primary studies
Baker, Jennifer A and Pereira, Gavin (2015) The efficacy of Botulinum Toxin A on improving ease of care in the upper and lower limbs: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. Clinical rehabilitation 29(8): 731-40	- Systematic review used as source of primary studies

Study	Code [Reason]
Brashear, A. (2018) Evidence for the use of BoNT in the lower extremity. Toxicon 156(supplement1): 11-s12	- Conference abstract/trial registry record
Brashear, A, Marciniak, C, Edgley, S et al. (2016) Extension study to assess the safety and efficacy of repeated abobotulinumtoxina injections in adults with upper limb spasticity. Neurology 86(16suppl1)	- Conference abstract/trial registry record
Chan, Aaron K; Finlayson, Heather; Mills, Patricia B (2017) Does the method of botulinum neurotoxin injection for limb spasticity affect outcomes? A systematic review. Clinical rehabilitation 31(6): 713-721	- Comparator in study does not match that specified in this review protocol
Chen, J.J., Dashtipour, K., Walker, H. et al. (2015) Systematic literature review of abobotulinumtoxinA in clinical trials for lower limb spasticity. Pharmacotherapy 35(11): e197-e198	- Duplicate reference
Chen, J.J., Dashtipour, K., Walker, H. et al. (2015) Systematic literature review of abobotulinumtoxina in clinical trials for lower limb spasticity. Journal of Pharmacy Practice 28(3): 329	- Systematic review used as source of primary studies
Chen, J.J., Walker, H., Han, Y. et al. (2014) A mixed treatment comparison to compare the efficacy of botulinum toxin type a treatments for upper limb spasticity. Pharmacotherapy 34(10): e213	- Conference abstract/trial registry record
Costello, E (1999) The effects of spasticity reduction with baclofen on ambulation proficiency of individuals with multiple sclerosis. Dissertation/ thesis: 89p	- Unavailable thesis
Dashtipour, K., Camba, G.C., Chen, J.J. et al. (2016) Systematic literature review of abobotulinumtoxinA in randomized, controlled clinical trials for adult lower limb spasticity. PM and R 8(9supplement): 227-s228	- Conference abstract/trial registry record
Dashtipour, Khashayar, Chen, Jack J, Walker, Heather W et al. (2016) Systematic Literature Review of AbobotulinumtoxinA in Clinical Trials for Lower Limb Spasticity. Medicine 95(2): e2468	- Systematic review used as source of primary studies

Study	Code [Reason]
Dressler, Dirk, Bhidayasiri, Roongroj, Bohlega, Saeed et al. (2017) Botulinum toxin therapy for treatment of spasticity in multiple sclerosis: review and recommendations of the IAB-Interdisciplinary Working Group for Movement Disorders task force. Journal of neurology 264(1): 112-120	- Systematic review used as source of primary studies
Ergul, M.; Nodehi Moghadam, A.; Soh, R. (2020) The effectiveness of interventions targeting spasticity on functional clinical outcomes in patients with multiple sclerosis: a systematic review of clinical trials. European Journal of Physiotherapy	- Systematic review used as source of primary studies
Farag, Jordan, Reebye, Rajiv, Ganzert, Carl et al. (2020) Does casting after botulinum toxin injection improve outcomes in adults with limb spasticity? A systematic review. Journal of rehabilitation medicine 52(1): jrm00005	- Study does not contain an intervention relevant to this review protocol
Francisco, GE, Wissel, J, Banach, M et al. (2020) The PATTERN customized study design: a novel method to investigate the efficacy and safety of incobotulinumtoxina in the treatment of lower limb spasticity in adults. International society of physical and rehabilitation medicine (ISPRM) 2020	- Conference abstract/trial registry record
Fu, Xiying, Wang, Yanqiao, Wang, Can et al. (2018) A mixed treatment comparison on efficacy and safety of treatments for spasticity caused by multiple sclerosis: a systematic review and network meta-analysis. Clinical rehabilitation 32(6): 713-721	- Systematic review used as source of primary studies
Grigoriu, A.I., Dinomais, M., Remy-Neris, O. et al. (2015) Impact of injection-guiding techniques on the effectiveness of botulinum toxin for the treatment of focal spasticity and dystonia: A systematic review. Annals of Physical and Rehabilitation Medicine 58(suppl1): e84	- Conference abstract
Guarany, FC, Picon, PD, Guarany, NR et al. (2013) A double-blind, randomised, crossover trial of two botulinum toxin type a in patients with spasticity. PloS one 8(2): e56479	- Population not relevant to this review protocol
Hardie, RJ (2000) Botulinum toxin in muscle spasticity. Journal of neurology neurosurgery and psychiatry 68(6): 689-690	- Not a peer-reviewed publication

Study	Code [Reason]
Hu, G-C (2017) Comparing the Radial Extracorporeal Shock Waves and Botulinum Toxin Injection for Spasticity.	- Conference abstract/trial registry record
Intiso, Domenico; Santamato, Andrea; Di Rienzo, Filomena (2017) Effect of electrical stimulation as an adjunct to botulinum toxin type A in the treatment of adult spasticity: a systematic review. Disability and rehabilitation 39(21): 2123-2133	- Systematic review used as source of primary studies
Ipsen (2011) Dysport® Adult Upper Limb Spasticity.	- Conference abstract/trial registry record
Ipsen Pharma, SAS (2017) Dysport® adult lower limb spasticity study.	- Conference abstract/trial registry record
Ipsen Pharma, SAS (2017) Dysport® adult lower limb spasticity follow-on study.	- Conference abstract/trial registry record
Jean-Michel, Gracies, MD, Mara, Lugassy et al. (2009) Botulinum Toxin Dilution and Endplate Targeting inSpasticity: a Double-Blind Controlled Study. Archives of physical medicine and rehabilitation 90: 9-16	- Population not relevant to this review protocol
Kaba, S., Aikman, M., Kantor, D. et al. (2016) A randomized, double-blind, parallel group study to compare the safety and efficacy of arbaclofen extended release tablets to placebo and baclofen for the treatment of spasticity in patients with multiple sclerosis. Journal of Managed Care and Specialty Pharmacy 22(4asuppl): 69	- Conference abstract/trial registry record
Kaba, S.; Kantor, D.; Tyle, P. (2016) The safety and efficacy of arbaclofen extended release tablets in the treatment of spasticity in patients with multiple sclerosis. Archives of Physical Medicine and Rehabilitation 97(10): e91	- Full text paper not available
Kanovsky, P., Pulte, I., Grafe, S. et al. (2013) Significant and sustained efficacy of incobotulinumtoxinA in upper limb spasticity. Toxicon 68: 115-116	- Conference abstract/trial registry record
Kantor, D., Wynn, D., Dentiste, A. et al. (2016) A randomized, double-blind, parallel group study to compare the safety and efficacy of arbaclofen extended release tablets to placebo and baclofen for the treatment of spasticity in	- Conference abstract/trial registry record

Study	Code [Reason]
patients with multiple sclerosis. Neurology 86(16suppl1)	
Kostenko, EV and Boiko, AN (2018) Treatment of a spastic increase of muscle tone in multiple sclerosis with botulinum toxin. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova 118(7): 89-93	- Study not reported in English
Kuen, Iam, Kwok Kwong, Lau, Kar Kui, So et al. (2012) Can Botulinum Toxin decrease carer Burden in Long Term Care Residents with Upper Limb Spasticity. JAMDA 13: 477-484	- Population not relevant to this review protocol
Kwakkel, G and Meskers, CGM (2015) Botulinum toxin A for upper limb spasticity. Lancet neurology 14: 969-971	- Review article but not a systematic review
Lam, K., Wong, D., Tam, C.K. et al. (2015) Ultrasound and electrical stimulator-guided obturator nerve block with phenol in the treatment of hip adductor spasticity in long-term care patients: A randomized, triple blind, placebo controlled study. Journal of the American Medical Directors Association 16(3): 238-246	- Population not relevant to this review protocol
Lam, K, Lau, K K, So, K K et al. (2016) Use of botulinum toxin to improve upper limb spasticity and decrease subsequent carer burden in long-term care residents: a randomised controlled study. Hong Kong medical journal = Xianggang yi xue za zhi 22suppl2: 43-5	- Population not relevant to this review protocol
Lam, K, Lau, KK, So, KK et al. (2012) Can botulinum toxin decrease carer burden in long term care residents with upper limb spasticity? A randomized controlled study. Journal of the american medical directors association 13(5): 477-484	- Population not relevant to this review protocol
Lannin, N, English, C, Levy, T et al. (2012) Design and feasibility of a randomized clinical trial to evaluate the effect of intensive rehabilitation following botulinum toxin injections in neurological patients with spasticity. Neurorehabilitation and neural repair 26(6): 717	- Conference abstract/trial registry record
Lazorthes, Y, Sallerin, B, Verdie, J-CI et al. (1998) Treatment of the spasticity by intrathecal administration of baclofen. Neuro-Chirurgie 44(3): 201-208	- Study not reported in English

Study	Code [Reason]
Li, N (2015) ASIS for Botox in Upper Limb Spasticity (ASISinULS).	- Conference abstract/trial registry record
Lotito, G, Bensoussan, L, Delarque, A et al. (2011) Botulinum toxin for the treatment of spastic equinovirus foot in adults: effect on gait parameters. Comparative randomized double-blind trial versus placebo. Annals of physical and rehabilitation medicine 54(s1): e137-e138	- Conference abstract/trial registry record
Maggio, R.; Lalli, S.; Albanese, A. (2016) Direct comparisons for botulinum neurotoxins in movement disorders. European Journal of Neurology 23(suppl2): 655	- Comparator in study does not match that specified in this review protocol
Mathevon, L., Declemy, A., Laffont, I. et al. (2019) Immunogenicity induced by botulinum toxin injections for limb spasticity: A systematic review. Annals of Physical and Rehabilitation Medicine 62(4): 241-251	- Population not relevant to this review protocol
McCrory, Paul, Turner-Stokes, Lynne, Baguley, Ian et al. (2009) Botulinum toxin A for the treatment of upper limb spasticity; A multi-centred randomized placebo controlled study of the effects on quality of life and other person centred outcomes. Journel of rehabilitation medicine 41: 536-544	- Population not relevant to this review protocol
McGuire, J.R.; Hast, M.; Hanschmann, A. (2018) Safety of incobotulinumtoxina in adult spasticity: Results from a pooled analysis of randomized, prospective, clinical studies. PM and R 10(9supplement): 35	- Conference abstract/trial registry record
Mills, Patricia Branco, Finlayson, Heather, Sudol, Malgorzata et al. (2016) Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Clinical rehabilitation 30(6): 537-48	- Population not relevant to this review protocol
Moore, E., Williams, G., Olver, J. et al. (2015) The effectiveness of therapy on outcome following BoNT-a injection for focal spasticity in adults with neurological conditions-systematic review. Physiotherapy (United Kingdom) 101(suppl1): es1028-es1029	- Conference abstract
Nicholas, Richard and Chataway, Jeremy (2007) Multiple sclerosis. BMJ clinical evidence 2007	- Review article but not a systematic review

Study	Code [Reason]
Nicholas, Richard and Chataway, Jeremy (2009) Multiple sclerosis. BMJ clinical evidence 2009	- Systematic review used as source of primary studies
Nicholas, Richard and Rashid, Waqar (2012) Multiple sclerosis. BMJ clinical evidence 2012	- Systematic review used as source of primary studies
Otero-Romero, Susana, Sastre-Garriga, Jaume, Comi, Giancarlo et al. (2016) Pharmacological management of spasticity in multiple sclerosis: Systematic review and consensus paper. Multiple sclerosis (Houndmills, Basingstoke, England) 22(11): 1386-1396	- Systematic review used as source of primary studies
Paisley, S, Beard, S, Hunn, A et al. (2002) Clinical effectiveness of oral treatments for spasticity in multiple sclerosis: a systematic review. Multiple sclerosis (Houndmills, Basingstoke, England) 8(4): 319-329	- Systematic review used as source of primary studies
Paoloni, Marco, Giovannelli, Morena, Mangone, Massimiliano et al. (2013) Does giving segmental muscle vibration alter the response to botulinum toxin injections in the treatment of spasticity in people with multiple sclerosis? A single-blind randomized controlled trial. Clinical rehabilitation 27(9): 803-12	- Comparator in study does not match that specified in this review protocol
Polo, KB and Jabbari, B (1994) Botulinum toxin-A improves the rigidity of progressive supranuclear palsy. Annals of neurology 35(2): 237-239	- Study design not relevant to this review protocol
Pong, Y-P (2015) Botulinum toxin injections by ultrasounds guidance and stretching exercise in spastic toe clawing.	- Conference abstract/trial registry record
Safarpour, Yasaman; Mousavi, Tahereh; Jabbari, Bahman (2017) Botulinum Toxin Treatment in Multiple Sclerosis-a Review. Current treatment options in neurology 19(10): 33	- Systematic review used as source of primary studies
Schnitzler, A., Rousset, L., de Oliveira, L. et al. (2018) Economic benefits of adult upper limb spasticity treatment with abobotulinumtoxinA compared with onabotulinumtoxinA or incobotulinumtoxinA: Analysis of a real-life setting in France. Toxicon 156(supplement1): 103-s104	- Conference abstract/trial registry record

Study	Code [Reason]
Shaygannejad, Vahid, Janghorbani, Mohsen, Vaezi, Atefeh et al. (2013) Comparison of the effect of baclofen and transcutaneous electrical nerve stimulation for the treatment of spasticity in multiple sclerosis. Neurological research 35(6): 636-41	- Study does not contain an intervention relevant to this review protocol
Simpson, D.; Hast, M.; Hanschmann, A. (2018) Safety of incobotulinumtoxina in adult spasticity: Results from a pooled analysis of randomized, prospective, clinical studies. Neurology 90(15supplement1)	- Conference abstract/trial registry record
Thanikachalam, Vivekanand, Phadke, Chetan P, Ismail, Farooq et al. (2017) Effect of Botulinum Toxin on Clonus: A Systematic Review. Archives of physical medicine and rehabilitation 98(2): 381-390	- Population not relevant to this review protocol
Waddell, B., Grieve, K., Walker, P. et al. (2012) Gabapentin for spasticity in multiple sclerosis-lack of efficacy data using the Wartenburg's Pendulum test. Multiple Sclerosis 18(4suppl1): 97-98	- Conference abstract

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 45: Studies excluded from the health economic review

Reference	Reason for exclusion
Bensmail 2009[1]	Excluded due to a combination of applicability and methodological limitations. Study did not include QALYs, no discounting reported, does not include all comparators in protocol and usual care poorly defined. Clinical effectiveness measured in analysis using a combined outcome of treatment success which includes outcomes not included in the clinical review protocol and unpublished data making it impossible to assess whether the evidence is reflective of the clinical review. Costs from a French healthcare perspective dating from 2006 and so may not reflect current NHS costs. Limited sensitivity analyses conducted and a potential conflict of interest as one of the authors linked to manufacturer of baclofen pump.

Appendix J – Research recommendations – full details

J.1 Research recommendation

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of pharmacological interventions for generalised spasticity?

J.1.1 Why this is important

Spasticity is a common symptom affecting up to 80% of people with MS. This may lead to muscle spasms, which are sudden, involuntary, often painful movements affecting any part of the body. Spasticity can range from a feeling of tightness or stiffness in one or more limbs to a tightening of the muscles throughout the body which is so severe that the person is unable to move voluntarily and may be confined to a wheelchair or bed. If not managed properly, it can lead to the secondary complications of permanent muscle contractures with pain and an increased risk of pressure sores. Although medications exist which can reduce spasticity, many people may develop side effects, such as drowsiness or confusion and there may be wide variations in the dosages of medication that people require manage their symptoms. There are a number of different oral medications that are licensed for the treatment of spasticity in MS but it is not known which are the most clinically effective and cost effective.

J.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Spasticity affects up to 80% of people with multiple sclerosis, with up to 30% reporting moderate to severe spasticity. Spasticity can have a significant negative effect on quality of life and can impact on mobility, sleep, sexual function, energy level, hygiene, employment, pain, fatigue, mood and social function. It can also lead to the development of avoidable yet costly secondary complications such as pressure ulcers and contractures and increase the burden of care. Careful management of this condition, including correct dosing of medication, is vital as people with MS may use their spasticity to aid function, such as standing, transferring and walking. In the pharmacological treatment of spasticity having evidence on which to make treatment decisions is important in reducing risks of side effects and ensuring that people are receiving the most clinically appropriate treatment.
Relevance to NICE guidance	The current NICE guideline makes some recommendations about the pharmacological treatment of spasticity in people with MS. This is based on a very small number of studies with no direct head-to-head comparisons of the efficacy and safety of these medications. Having this information would generate knowledge and evidence so that future guidelines would be clearer on the pharmacological management of spasticity in terms of deciding between the different treatments that are currently available

	and help to understand whether combinations of treatments are safe and effective.
Relevance to the NHS	There are 100,000 people with MS in the UK (MS Society). As up to 80 % of people with MS will experience spasticity during the course of their illness, the treatment and management of spasticity is a frequent issue for health professionals, people with MS and the people who care for them. Evaluating the clinical and cost-effectiveness of different pharmacological interventions will contribute to reducing the financial and personal cost of this condition. Evidence-based prescribing should reduce potential morbidity from side effects of less effective medication and reduce costs associated with continued prescribing of ineffective treatments.
National priorities	The National Service Framework for long term conditions supports the early management of symptoms
Current evidence base	Although there are a number of studies comparing oral medications used to treat spasticity against placebo or diazepam the only head-to-head studies have looked at tizanidine compared baclofen. In clinical practice many people with MS and spasticity may be prescribed a combination of different medications to treat their spasticity but there is no evidence at all as to which combinations and at which dosages.
Equality considerations	None identified.

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J.1.32 Modified PICO table

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Population	<u>Inclusion</u> Adults (≥18 years) with MS, including people receiving palliative care. <u>Exclusion:</u> Children and young people (≤18 years).
Intervention	• Baclofen (oral) (Lioresal)- used more widely • Tizanidine (Zanaflex) • Gabapentin (Neurontin) • Dantrolene sodium (Dantrium) • Benzodiazepines (Diazepam, clonazepam) • Combinations of the above
Comparator	Interventions will be compared to each other (both within and between classes), to placebo/sham, or to usual care or no treatment.
Outcome	• Spasticity scales for example: o Modified Ashworth scale

	○ Tardieu Scale ○ Muscle Elastography MS Scale (MEMSs) ○ Fugl Meyer Scale (FMS) • Patient reported measures of spasticity for example: ○ Penn Spasm Frequency Scale ○ Numeric Rating Scale for Spasticity (NRS-S) ○ MS Spasticity Scale-88 (MSSS) ○ Patient-reported Impact of Spasticity Measure (PRISM) • Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale • Adverse effects of treatment for example: ○ Any adverse events ○ Adverse events leading to withdrawal ○ Drowsiness ○ Weakness ○ Nausea ○ Mobility • Pain scales for example visual analogue scale (VAS) • Improvement in sleep • Comfort and posture positioning (self reported) • Functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), the Functional Assessment of Multiple Sclerosis (FAMS), the National Fatigue Index (NFI) or the MS walking scale. • Impact on patients/ carers **Follow up:** • 3-6 months • >6 months – 1 year
Study design	RCT
Timeframe	Medium term
Additional information	

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