National Institute for Health and Care Excellence

Final

# Multiple sclerosis in adults: management

## [l] Evidence review for pharmacological management of ataxia and tremor

*NICE guideline NG220*

*Evidence reviews underpinning research recommendations in the NICE guideline*

*June 2022*

*Final*

*National Institute for Health and Care Excellence*

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# 1 Pharmacological management of ataxia and tremor

## 1.1 Review question

For adults with MS, what is the clinical and cost effectiveness of interventions for ataxia and tremor?

### 1.1.1 Introduction

Multiple Sclerosis (MS) can cause ataxia (which means lack of coordination) and tremor which can be disabling. The prevalence is unclear with some reports suggesting that tremor can occur in up to 80% of people with MS at some stage of their disease. These symptoms may make simple activities (for example, dressing and eating) very challenging. In addition, it can have significant emotional and social impact.

They are difficult symptoms to treat, and since the Food and Drug Administration (FDA) or European Medicines Agency (EMA) have not approved any drug to treat tremor and ataxia related to MS, the MS specialists may try different medications, which are used off-label. The aim of this review was to determine the clinical and cost effectiveness of pharmacological treatments that clinicians may consider when treating ataxia and tremor in people with MS.

Non-pharmacological agents are not currently used to treat ataxia and tremor in the MS population and this review therefore focuses on pharmacological interventions.

### 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** | Inclusion:<br>Adults (≥18 years) with MS, including people receiving palliative care.<br><br>Exclusion:<br>Children and young people (≤18 years). |
| **Interventions** | Pharmacological interventions:<br>• Baclofen (oral/intrathecal)<br>• Isoniazid<br>• Antiepileptics for example Carbamazepine<br>• beta blockers for example Propranolol<br>• benzodiazepines for example Clonazepam<br>• Primidone<br>• Ondansetron<br>• Fampridine<br>• Botulinum toxin<br>• Gabapentin<br>• Or combinations of the above |
| **Comparisons** | Interventions will be compared to each other (both within and between classes), placebo/sham, or usual care with no pharmacological treatment. |

| | |
|---|---|
| **Outcomes** | All outcomes are considered equally important for decision making and therefore have all been rated as critical.<br><br>• Health-related Quality of Life (validated), for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale.<br>• Ataxia measurement scales:<br>o International Cooperative Ataxia Rating Scale (ICARS)<br>• Tremor rating scales (TRS),<br>o Fahn<br>o SARA<br>o 9-hole peg test<br>o Archimedean Spiral<br>• 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) or + mobility scales<br>• Adverse effects of treatment:<br>• Withdrawal due to adverse effects (e.g., fatigue)<br>• Patient-reported outcomes, for example symptoms of ataxia and tremor or adverse events.<br>• Impact on carers.<br><br>Follow-up:<br>- At 6 months (if multiple time points are reported, we will only record the closest reported time point up to 6 months)<br>• >6 months - 12 months (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.<br>Cross-over trials will also be considered for inclusion if they have an appropriate washout period of at least 1 week.<br>Published NMAs and IPDs will be considered for inclusion. |

### 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

Two randomised controlled studies, Boonstra 2020[2] and Van der Walt[2, 5] were included in the review. One was a parallel and one a cross-over trial; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

**Population**

Boonstra 2020[2] included people with relapsing-remitting and secondary-progressive multiple sclerosis and unilateral upper limb tremor. Van der Walt [5] included people with relapsing remitting and secondary progressive multiple sclerosis with disabling arm tremor.

**Interventions and comparisons covered by the evidence**

Both studies compared Botulinum toxin type A (BoNT-A) with placebo[2, 5].

No relevant randomised controlled trials investigating the following interventions were identified:

- Baclofen (oral/intrathecal)
- Isoniazid
- Antiepileptics for example Carbamazepine
- beta blockers for example Propranolol
- benzodiazepines for example Clonazepam
- Primidone
- Ondansetron
- Fampridine
- Gabapentin

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

### 1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

### 1.1.5 Summary of studies included in the effectiveness evidence

**Table 2: Summary of studies included in the evidence review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Boonstra, 2020[2]<br><br>Randomised controlled trial<br><br>N= 43<br><br>Australia | **Botulinum toxin A**<br>n=21<br><br>An expert movement disorder neurologist administered targeted injections of BoNT-A (Botox; Alergan Australia Inc) after a careful assessment of the tremor pattern. A maximum dose of 150 IU BoNT-A was injected at the baseline visit.<br>An unblinded pharmacist prepared in equal volumes 100 units of BoNT-A diluted per 2mL 0.9% sterile saline or 2mL 0.9% sterile saline syringes. To optimise targeted treatment, injections were guided using the Dantec Clavis handheld electromyogram (EMG) and stimulation device (Natus Neurology).<br><br>**Placebo:**<br>n=22<br>An expert movement disorder neurologist administered targeted injection of placebo after a careful assessment of the tremor pattern. A maximum dose of 150 IU normal saline placebo was injected at the baseline visit. | Adults with relapsing-remitting and secondary-progressive multiple sclerosis and unilateral upper limb tremor.<br><br>**Age:** mean (SD):<br>Botulinum toxin 45.9 (13.5)<br>Placebo 47 (9.35)<br><br>**EDSS mean score** (SD)<br>Botulinum toxin 4.41 (1.76)<br>Placebo 3.97 (1.71)<br><br>**MS Type**:<br>Majority relapsing-remitting and secondary progressive in both groups. | Tremor severity (Bain score)<br>Handwriting<br>Archimedes spiral drawing | New study published since previous guideline.<br><br>Follow-up 12 weeks |
| Van Der Walt, 2012[5] | **Botulinum toxin type A** | Adults with MS | Quality of life QUEST score | Included in the previous guideline. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Randomised double blind cross-over trial.<br><br>N=25<br>(36 limbs as 10 people were bilateral)<br><br>Australia | Maximum dose of 100IU botulinum toxin injected at baseline. Injections targeted at agonist and antagonist muscles involved in the tremor pattern. Treatment given under EMG guidance.<br><br>**Placebo:**<br>Same dose of identical placebo injected at baseline. Injections targeted at agonist and antagonist muscles involved in the tremor pattern. Treatment given under EMG guidance | **Age**<br>mean age 49.6 years; duration tremor 6.5(5.1) years.<br><br>**EDSS** median (IQR):5.5(4-6.5)<br><br>**MS type:**<br>Relapsing remitting 6 (26%), Secondary progressive 17 (74%). | Bain composite tremor score (0-10)<br>Bain writing score (0-10)<br>Bain Archimedes spiral (0-10)<br>CRST writing (0-4)<br>CRST drawing (0-4)<br>ICARS Archimedes spiral (0-4)<br>CRST pouring (0-4)<br>Drinking from cup (0-4)<br>9-hole peg test<br>Kinetic tremor severity(0-4)<br>CRST action tremor arm (0-4)<br>CRST action tremor amplitude (cm)<br>CARS finger-finger test<br>Postural tremor severity (0-4)<br>Batwing position tremor (0-4)<br>CRST postural tremor arm (0-4)<br>CRST postural tremor amplitude (cm) | Follow-up<br>12 weeks<br><br>Reports Median (IQR) only |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | Ataxia rating scores - SARA score change from baseline<br>Adverse events - Muscle weakness | |

### 1.1.6 Summary of the effectiveness evidence

**Table 3: Clinical evidence summary: BoNT-A (Botox) versus placebo (new study identified in current update)**

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with control (placebo) | Risk difference with BoNT-A |
| Tremor severity (Bain score, 0 to 10)<br>Lower values indicate better | 43<br>(1 RCT) follow up: 12 weeks | ⨁⨁◯◯<br>LOW [a,b] | - | The mean tremor severity (Bain score, 0 to 10) was -0.60 | MD 0.19 lower (0.92 lower to 0.54 higher) |
| Handwriting (writing a standardised sentence)<br>Lower values indicate better | 43<br>(1 RCT)<br>follow up: 12 weeks | ⨁⨁◯◯<br>LOW [a,c] | - | The mean handwriting (writing a standardised sentence) was -0.25 | MD 0.28 lower (0.9 lower to 0.34 higher) |
| Archimedes spiral drawing on a pre-drawn pattern<br>Lower values indicate better | 43<br>(1 RCT)<br>follow up: 12 weeks | ⨁⨁◯◯<br>LOW [a,d] | - | The mean archimedes spiral drawing on a pre-drawn pattern was -0.25 | MD 0.38 lower (1.2 lower to 0.44 higher) |

a. Downgraded by 1 increment due to concerns about high risk of bias in the randomisation process.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group median SD for % baseline change by 0.5 and were ±0.65

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group median SD for % baseline change by 0.5 and were ±0.60

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group median SD for % baseline change by 0.5 and were ±0.66

**Table 4: Clinical evidence summary: Botulinum versus placebo (study included in previous version of the guideline)**

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Median (IQR) change from baseline (continuous outcomes) or event rate | | Effect | |
|---|---|---|---|---|---|---|---|
| | | | | Placebo | Botulinum A | P-value for Wilcoxon signed ranks | Absolute |
| Quality of Life QUEST score<br>Higher values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕◯◯<br>LOW a,b | - | -4(-12 to 1) | 0(-4 to 6) | 0.1136 | NA |
| Bain composite tremor score (0-10)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(-1 to 1) | -2(-2 to -1) | 0.0001 | NA |
| Bain writing score (0-10)<br>Lower values indicate better | 22<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | -1(-1 to 0) | 0.002 | NA |
| Bain Archimedes spiral (0-10)<br>Lower values indicate better | 22<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 1) | -1(-2 to 0) | 0.0007 | NA |
| CRST writing (0-4)<br>Lower values indicate better | 22<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕◯◯<br>LOW a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.197 | NA |
| CRST drawing (0-4)<br>Lower values indicate better | 22<br>(1 RCT) | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | -0.5(-1 to 0) | 0.024 | NA |

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Median (IQR) change from baseline (continuous outcomes) or event rate | | Effect | |
|---|---|---|---|---|---|---|---|
| | | | | Placebo | Botulinum A | P-value for Wilcoxon signed ranks | Absolute |
| | follow-up: 12 weeks | | | | | | |
| ICARS Archimedes spiral (0-4)<br>Lower values indicate better | 22<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕◯◯<br>LOW a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.3351 | NA |
| CRST pouring (0-4)<br>Lower values indicate better | 29<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕◯◯<br>LOW a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.0628 | NA |
| Drinking from cup (0-4<br>Lower values indicate better | 29<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.0089 | NA |
| 9-hole peg test<br>Lower values indicate better | 28<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(-6 to 4) | -4.5(-14 to -1) | 0.0195 | NA |
| Kinetic tremor severity (0-4)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 1) | -1(-1 to 0) | <0.0001 | NA |
| CRST action tremor arm (0-4)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.021 | NA |

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Median (IQR) change from baseline (continuous outcomes) or event rate | | Effect | |
|---|---|---|---|---|---|---|---|
| | | | | Placebo | Botulinum A | P-value for Wilcoxon signed ranks | Absolute |
| CRST action tremor amplitude (cm)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0.5) | -1(-2 to 0) | 0.0012 | NA |
| ICARS finger-finger test<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕◯◯<br>LOW a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.4274 | NA |
| Postural tremor severity (0-4)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | -1(-1 to 0) | 0.0161 | NA |
| Batwing position tremor (0-4)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | -1(-1 to 0) | 0.0268 | NA |
| CRST postural tremor arm (0-4)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0) | 0(-1 to 0) | 0.0076 | NA |
| CRST postural tremor amplitude (cm)<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⊕⊕⊕◯<br>MODERATE a,b | - | 0(0 to 0.5) | -0.5(-5 to 0) | 0.0077 | NA |

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Median (IQR) change from baseline (continuous outcomes) or event rate | | Effect | |
|---|---|---|---|---|---|---|---|
| | | | | Placebo | Botulinum A | P-value for Wilcoxon signed ranks | Absolute |
| Ataxia rating scores - SARA score change from baseline<br>Lower values indicate better | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⨁⨁◯◯<br>LOW a,b | - | 0.5(1.5 to 2) | -2(-3 to 0) | 0.089 | NA |
| Adverse events - Muscle weakness | 33<br>(1 RCT)<br>follow-up: 12 weeks | ⨁⨁⨁◯<br>MODERATE a,c | RR: 7 (1.72 TO 28.41) | 2/33 (6.1%) | 14/33 (42.4%) | NA | 364 more per 1000 (from 44 more to 1000 more) |

a. Downgraded by 1 increment because the study had attrition bias

b. Because of the lack of confidence intervals or absolute effect sizes, imprecision was based on the Wilcoxon signed ranks test. If $p<0.05$ it was rated as precise and if $p>0.05$ as seriously imprecise

c. This outcome was rated as precise because neither confidence interval crossed either of the default MIDs (0.80 and 1.25)

See Appendix F for full GRADE tables

## 1.1.7 Economic evidence

### 1.1.7.1 Included studies

No health economic studies were included.

### 1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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

## 1.1.8 Summary of included economic evidence

None.

## 1.1.9 Economic model

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

## 1.1.10 Unit costs

Relevant unit costs for botulinum toxin A solution for injection are provided below to aid consideration of cost effectiveness.

**Table 5: Unit costs for botulinum toxin type A**

| Medicinal form | 50 units per vial | 100 units per vial | 200 units per vial | 300 units per vial | 500 units per vial |
|---|---|---|---|---|---|
| Bocouture | £72 | £230 | n/a | n/a | n/a |
| Botox | £77 | £138 | £276 | n/a | n/a |
| Xeomin | £72 | £130 | £260 | n/a | n/a |
| Dysport | n/a | n/a | n/a | £92 | £308 |

*Source/Note: All solution for injection. BNF online, accessed June 2021[1].*

Of note different botulinum toxin type A products have different potency and the units are not equivalent. A paper by Scaglione 2016[4] reports the following clinical conversion ratios:

- Botox:Dysport 1:3
- Botox:Xeomin 1:1

Therefore, a dose of 300 units of Dysport is equivalent to 100 units of Botox. Bocouture was not included in this paper.

In addition, to the cost of the drug, there is a staff cost associated with the administration and both studies included in the clinical review reported that it was administered under electromyogram guidance. Boonsta 2020[2], also reposted using a stimulation device. All of these would increase the total cost associated with the use of botulinum toxin.

## 1.1.11 Evidence statements

### Clinical

For results that could be assessed using GRADE, see summary of evidence in Tables 3-4.

**Economic**

- No relevant economic evaluations were identified.

## 1.1.12 The committee's discussion and interpretation of the evidence

### 1.1.12.1. The outcomes that matter most

The committee considered all outcomes listed in the protocol to be critical and of equal importance in decision-making. These outcomes were Health-related Quality of Life such as EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale, ataxia measurement scales such as the International Cooperative Ataxia Rating Scale (ICARS); tremor rating scales such as Archimedean Spiral drawing; functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC); adverse effects of treatments and impact on carers.

The included studies reported on health-related quality of life using the Quality of Life in Essential Tremor Questionnaire (QUEST) and various tremor rating scores which were all reported at 12 weeks.

There were no relevant randomised controlled trials investigating Baclofen (oral/intrathecal), Isoniazid, antiepileptics, beta blockers, benzodiazepines, Primidone, Ondansetron, Fampridine or Gabapentin.

### 1.1.12.2 The quality of the evidence

Two randomised controlled studies (one parallel and one cross-over) were included in the review. One was a newly identified study and the other was already included in the previous guideline. Both studies compared Botulinum toxin type A with placebo at doses that reflect clinical practice. However, the data could not be pooled as one of the studies reported medians and interquartile ranges and the other reported mean differences.

The quality of the evidence was assessed by GRADE or a modified GRADE approach where means and IQRs were reported. When modified GRADE was used, particularly where there were no confidence intervals to assess imprecision and p values were used instead, the results were cautiously interpreted due to the limitations of this method. The overall GRADE rating for the evidence was found to be low or moderate. Downgrading was mainly due to risk of bias and imprecision. There was no indirectness in terms of follow up as the committee agreed that although the follow up was shorter than the 6 months indicated in the protocol, it was still clinically meaningful follow up time for the effect of the intervention to be seen. There was no inconsistency.

### 1.1.12.3 Benefits and harms

There was insufficient evidence for the committee to make any recommendations. Ataxia and tremor impact on a person's ability to carry out activities of daily living and treatment options are currently limited. It is therefore important to identify clinically effective treatments but in the absence of evidence, the variation in clinical practice and potential resource impact the committee were unable to make consensus recommendations. They acknowledged that botulinum toxin may still be used by some clinicians as a last resort and therefore did not make a 'do not offer' recommendation. The committee made a research recommendation to explore clinical and cost effectiveness of the interventions specified in the protocol.

### 1.1.12.4 Cost effectiveness and resource use

No health economic studies were identified. Unit cost of botulinum toxin was presented to aid the consideration of cost-effectiveness. The committee noted that it is very rarely used in clinical practice for the management of ataxia, but it was widely used for spasticity. The committee discussed that in those that do receive botulinum toxin, they would also receive physiotherapy and so this would be an additional cost alongside the cost of botulinum toxin. The committee agreed to not make a recommendation due to the lack of clinical and health

economic evidence and use in current clinical practice. The committee did not want to include a do not offer recommendation as some physicians may use it as a last resort. The lack of recommendation will not change current practice and therefore there will be not resource impact.

### 1.1.13 Recommendations supported by this evidence review

This evidence review supports the research recommendation on ataxia and tremor.

### 1.1.14 References

1. 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.

2. Boonstra FMC, Evans A, Noffs G, Perera T, Jokubaitis V, Stankovich J et al. OnabotulinumtoxinA treatment for MS-tremor modifies fMRI tremor response in central sensory-motor integration areas. Multiple Sclerosis and Related Disorders. 2020; 40:101984

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

5. Van Der Walt A, Sung S, Spelman T, Marriott M, Kolbe S, Mitchell P et al. A double-blind, randomized, controlled study of botulinum toxin type A in MS-related tremor. Neurology. 2012; 79(1):92-99

# Appendices

## Appendix A – Review protocols

**Review protocol for non-pharmacological management of ataxia and tremor**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | CRD42021243139 |
| 1. | Review title | For adults with MS, what is the clinical and cost effectiveness of interventions for ataxia and tremor? |
| 2. | Review question | For adults with MS, what is the clinical and cost effectiveness of pharmacological interventions for ataxia and tremor? |
| 3. | Objective | To determine the most clinically effective pharmacological treatment for ataxia and tremor in patients with MS. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• Epistemonikos<br>Searches will be restricted by:<br>• Date limitations – databases will be searched from 2014 onwards (last search conducted for CG186) for all drugs. Searches for Gabapentin will be limited to 2000 onwards as this drug was not included in CG 186 and has only been used for ataxia and tremor in MS in the last 20 years.<br>• English language studies<br>• Human studies |

| | | |
|---|---|---|
| | | The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review.<br>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:<br>Adults (≥18 years) with MS, including people receiving palliative care.<br><br>Exclusion:<br>Children and young people (≤18 years). |
| 7. | Intervention | Pharmacological interventions:<br>• Baclofen (oral/intrathecal)<br>• Isoniazid<br>• Antiepileptics for example Carbamazepine<br>• beta blockers for example Propranolol<br>• benzodiazepines for example Clonazepam<br>• Primidone<br>• Ondansetron<br>• Fampridine<br>• Botox<br>• Gabapentin<br>  • Or combinations of the above |

| | | |
|---|---|---|
| 8. | Comparator | Interventions will be compared to each other (both within and between classes), placebo/sham, or usual care with no pharmacological treatment. |
| 9. | Types of study to be included | Systematic reviews of RCTs and RCTs will be considered for inclusion.<br><br>Cross-over trials will also be considered for inclusion if they have an appropriate washout period of at least 1 week.<br><br>Published NMAs and IPDs will be considered for inclusion. |
| 10. | Other exclusion criteria | Non-English language studies.<br><br>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.<br><br>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 | Ataxia and tremor in people with MS can be disabling. It is thought that tremor may occur in up to 80% of people with MS at some stage of the disease. There were no recommendations on pharmacological management of ataxia and tremor in CG186 as there was insufficient evidence. The review will evaluate any new evidence that has emerged that may be useful to make recommendations in this area. |
| 12. | Primary outcomes (critical outcomes) | All outcomes are considered equally important for decision making and therefore have all been rated as critical.<br><br>• Health-related Quality of Life (validated), for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale.<br>• Ataxia measurement scales: |

| | | |
|---|---|---|
| | | ○ International Cooperative Ataxia Rating Scale (ICARS)<br>• Tremor rating scales (TRS),<br>○ Fahn<br>○ SARA<br>○ 9-hole peg test<br>○ Archimedean Spiral<br>• 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) or + mobility scales<br>• Adverse effects of treatment:<br>• Withdrawal due to adverse effects (e.g., fatigue)<br>• Patient-reported outcomes, for example symptoms of ataxia and tremor or adverse events.<br>• Impact on carers.<br><br>Follow-up:<br>- At 6 months (if multiple time points are reported, we will only record the closest reported time point up to 6 months)<br>• >6 months - 12 months (data from >1 year follow up may be included but will be downgraded) |
| 13. | Secondary outcomes (important outcomes) | Not applicable – see note 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. |

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| | | A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).<br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br>• papers were included /excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br>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.<br>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.<br>The following checklist will be used according to study design being assessed:<br>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>• 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.<br>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.<br>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 |

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| | | 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.<br><br>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.<br><br>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/<br><br>Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.<br><br>If sufficient data is available, meta-regression or NMA-meta-regression will be conducted.<br><br>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:<br>• According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS)<br>• According to disability (EDSS <6 and EDSS ≥6)<br>• Disease modifying treatment status (currently using and not currently using)<br>• Drug doses (standard doses vs non-standard doses which will be discussed and agreed with the GC prior to presenting the evidence to them)<br>• Routes of administration particularly baclofen (intrathecal vs oral)<br>• People receiving palliative care |

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| 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 | ☐ / ☐ |

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| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>MultipleSclerosisUpdate@nice.org.uk<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | | |
| 25. | Review team members | From the National Guideline Centre:<br>• Dr Sharon Swain [Guideline lead]<br>• Dr Saoussen Ftouh [Senior systematic reviewer]<br>• Nicole Downes [Systematic reviewer]<br>• Emma Carter [Health economist]<br>• Lina Gulhane [Information specialist]<br>• Emma Clegg [Information specialist<br>• 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 | | |

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| | | 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:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• 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 | | |
| 33. | Details of existing review of same topic by same authors | None | |
| 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 | |

**Health economic review protocol**

| 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.<br>• 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).<br>• 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.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• 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.<br>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.<br>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).[3]<br><br>**Inclusion and exclusion criteria**<br>• 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.<br>• 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.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion** |

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| | 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.<br><br>The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS (most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).<br>• OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis (most applicable).<br>• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be.<br>• 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'.<br>• Studies published before 2005 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.<br>*Quality and relevance of effectiveness data used in the health economic analysis:*<br>• 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. |

# Appendix B – Literature search strategies

This literature search strategy was used for the following review:

- The clinical and cost effectiveness of interventions for ataxia and tremor for adults with MS.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[3]

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.

The Gabapentin part of the search was limited to 2000 onwards as this drug was not included in CG 186 and has only been used for ataxia and tremor in MS in the last 20 years.

**Table 6: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 01 January 2014 – 08 September 2021 | Randomised controlled trials<br>Systematic review studies<br><br>Exclusions (animal studies, letters, comments, children) |
| | Gabapentin only 01 January 2000 – 08 September 2021 | |
| Embase (OVID) | 01 January 2014 – 08 September 2021 | Randomised controlled trials<br>Systematic review studies<br><br>Exclusions (animal studies, letters, comments, conference abstracts, children) |
| | Gabapentin only 01 January 2000 – 08 September 2021 | |
| The Cochrane Library (Wiley) | Cochrane Reviews 2014 to 2021 Issue 9 of 12 | None<br><br>Exclusions (conference abstracts & clinical trials) |
| | Gabapentin only 2000 to 2021 Issue 9 of 12 | |
| | CENTRAL 2014 to 2021 Issue 9 of 12 | |
| | Gabapentin only 2000 to 2021 Issue 9 of 12 | |
| Epistemonikos (The Epistemonikos Foundation) | 01 January 2014 – 08 September 2021 | Systematic Reviews<br>Exclusions (Cochrane Reviews) |
| | Gabapentin only 01 January 2000 – 08 September 2021 | |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp Multiple Sclerosis/ |
| 2. | ((multiple or disseminated) adj2 scleros*).ti,ab. |

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|---|---|
| 3. | encephalomyelitis disseminata.ti,ab. |
| 4. | MS.ti. |
| 5. | Myelitis, Transverse/ |
| 6. | transverse myelitis.ti,ab. |
| 7. | or/1-6 |
| 8. | letter/ |
| 9. | editorial/ |
| 10. | news/ |
| 11. | exp historical article/ |
| 12. | Anecdotes as Topic/ |
| 13. | comment/ |
| 14. | case report/ |
| 15. | (letter or comment*).ti. |
| 16. | or/8-15 |
| 17. | randomized controlled trial/ or random*.ti,ab. |
| 18. | 16 not 17 |
| 19. | animals/ not humans/ |
| 20. | exp Animals, Laboratory/ |
| 21. | exp Animal Experimentation/ |
| 22. | exp Models, Animal/ |
| 23. | exp Rodentia/ |
| 24. | (rat or rats or rodent or mouse or mice).ti. |
| 25. | or/18-24 |
| 26. | 7 not 25 |
| 27. | limit 26 to English language |
| 28. | (exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/) |
| 29. | 27 not 28 |
| 30. | gamma-aminobutyric acid/ or baclofen/ or pregabalin/ |
| 31. | ("4 aminobutanoic acid*" or "4 aminobutyric acid*" or "gamma aminobutyric acid*" or "hydrochloride gamma-aminobutyric*" or aminalon* or gammalon* or GABA or Baclofen* or baclophen* or "chlorophenyl adj gaba" or lioresal or pregabalin* or "3 isobutyl gaba" or "3-aminomethyl-5-methylhexanoic acid" or Alzain or Axalid or Lecaent or lyrica).ti,ab. |
| 32. | anti-bacterial agents/ or exp antitubercular agents/ |
| 33. | (antibacterial* or anti-bacterial* or antimycobacterial* or antitubercul* or anti-tubercul*).ti,ab. |
| 34. | exp Isoniazid/ |
| 35. | (Isoniazid or Ftivazide or Isonex or Isonicotinic* or Phthivazid* or Tubazide or INH or Tebesium* or Cemidon).ti,ab. |
| 36. | exp Anticonvulsants/ |
| 37. | (anti adj2 (epileptic* or convulsant* or seizure*)).ti,ab. |
| 38. | (antiepileptic* or anticonvulsant* or AEDs or antiseizure).ti,ab. |
| 39. | Benzodiazepines/ or Midazolam/ or Piracetam/ |
| 40. | (Acetazolamide or Diamox or Eytazox or Carbamazepine or tegretol or Carbazepin or Clobazam or Frisium or Perizam or Tapclob or Zacco or Epitol or Finlepsin or Neurotol or Amizepine or Eslicarbazepine or Zebinix or Oxcarbazepine or Trileptal or Ethosuximide or emeside or zarontin or Lacosamide or vimpat or Lamotrigine or |

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| | Lamictal or Levetiracetam or keppra or Desitrend or Nitrazepam or Mogadon or Perampanel or fycompa or Phenobarbital or Phenobarbitone or Primidone or mysoline or Liskantin or Phenytoin or Dilantin or epanutin or Retigabine or trobalt or Riluzole or Rilutek or Teglutik or Rufinamide or inovelon or Tiagabine or gabitril or Topiramate or topamax or sodium valproate or epilim or episenta or epival or valproic acid or convulex or depakote or Belvo or Syonell or vigabatrin or sabril* or "gamma vinyl gaba*" or "gamma vinyl gamma aminobutyric acid*" or Zonisamide or zonegran or Desizon or Benzodiazepine* or Clobazam or Clonazepam or rivotril or Diazepam or Diazemuls or Stesolid or Fosphenytoin or pro-epanutin or Lorazepam or Ativan or Midazolam or Hypnovel or Epistatus or buccolam or Phenobarbital or Phenytoin or Epanutin or Acetazolamide or diamox or Piracetam or nootropil).ti,ab. |
| 41. | exp Adrenergic beta-Antagonists/ |
| 42. | ((b or beta*) adj3 (block* or antagonist*)).ti,ab. |
| 43. | (propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim or Beta-Prograne).ti,ab. |
| 44. | exp Serotonin 5-HT3 Receptor Antagonists/ |
| 45. | (5-HT3 adj2 Antagonis*).ti,ab. |
| 46. | Ondansetron/ |
| 47. | (ondansetron or zofran or Dolasetron or Anzemet).ti,ab. |
| 48. | exp Botulinum Toxins/ |
| 49. | (botulin* or onabotulinumtoxin* or abobotulinumtoxin* or incobotulinumtoxin* or prabotulinumtoxin* or rimabotulinum*).ti,ab. |
| 50. | (dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc or Azzalure or Bocouture or Myobloc or Jeuveau).ti,ab. |
| 51. | Dantrolene/ or Methocarbamol/ or Tramadol/ or Temazepam/ or Flunitrazepam/ or Flurazepam/ or Nitrazepam/ |
| 52. | (dantrolene or dantrium or tizanidine or zanaflex or methocarbamol or robaxin or tramadol or Brimisol or Invodol or zamadol or zydol or larapam or mabron or marol or maxitram or tramquel or Tilodol or Tramulief or zeridame or tradorec or nitrazepam or temazepam or flunitrazepam or Flurazepam or dalmane or zaleplon or sonata or zolpidem or stilnoct or zoiclone or zimovane).ti,ab. |
| 53. | aminopyridines/ or *4-aminopyridine/ |
| 54. | (Fampyra or aminopyridine* or dalfampridine or fampridine* or pymadine or ampyra).ti,ab. |
| 55. | or/30-54 |
| 56. | 29 and 55 |
| 57. | Gabapentin/ |
| 58. | (gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab. |
| 59. | or/57-58 |
| 60. | 29 and 59 |
| 61. | randomized controlled trial.pt. |
| 62. | controlled clinical trial.pt. |
| 63. | randomi#ed.ti,ab. |
| 64. | placebo.ab. |
| 65. | randomly.ti,ab. |
| 66. | Clinical Trials as topic.sh. |
| 67. | trial.ti. |

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| 68. | or/61-67 |
| 69. | Meta-Analysis/ |
| 70. | exp Meta-Analysis as Topic/ |
| 71. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 72. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 73. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 74. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 75. | (search* adj4 literature).ab. |
| 76. | (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. |
| 77. | cochrane.jw. |
| 78. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 79. | or/69-78 |
| 80. | 56 and (68 or 79) |
| 81. | 60 and (68 or 79) |
| 82. | 80 or 81 |

**Embase (Ovid) search terms**

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|---|---|
| 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. | letter.pt. or letter/ |
| 9. | note.pt. |
| 10. | editorial.pt. |
| 11. | (conference abstract or conference paper).pt. |
| 12. | case report/ or case study/ |
| 13. | (letter or comment*).ti. |
| 14. | or/8-13 |
| 15. | randomized controlled trial/ or random*.ti,ab. |
| 16. | 14 not 15 |
| 17. | animal/ not human/ |
| 18. | nonhuman/ |
| 19. | exp Animal Experiment/ |
| 20. | exp Experimental Animal/ |
| 21. | animal model/ |
| 22. | exp Rodent/ |
| 23. | (rat or rats or rodent* or mouse or mice).ti. |
| 24. | or/16-23 |
| 25. | 7 not 24 |
| 26. | limit 25 to English language |

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|---|---|
| 27. | (exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/) |
| 28. | 26 not 27 |
| 29. | 4 aminobutyric acid/ |
| 30. | baclofen/ |
| 31. | pregabalin/ |
| 32. | ("4 aminobutanoic acid*" or "4 aminobutyric acid*" or "gamma aminobutyric acid*" or "hydrochloride gamma-aminobutyric*" or aminalon* or gammalon* or GABA or Baclofen* or baclophen* or "chlorophenyl adj gaba" or lioresal or pregabalin* or "3 isobutyl gaba" or "3-aminomethyl-5-methylhexanoic acid" or Alzain or Axalid or Lecaent or lyrica).ti,ab. |
| 33. | antiinfective agent/ |
| 34. | exp tuberculostatic agent/ |
| 35. | (antibacterial* or anti-bacterial* or antimycobacterial* or antitubercul* or anti-tubercul*).ti,ab. |
| 36. | exp isoniazid/ |
| 37. | (Isoniazid or Ftivazide or Isonex or Isonicotinic* or Phthivazid* or Tubazide or INH or Tebesium* or Cemidon).ti,ab. |
| 38. | exp anticonvulsive agent/ |
| 39. | (anti adj2 (epileptic* or convulsant* or seizure*)).ti,ab. |
| 40. | (antiepileptic* or anticonvulsant* or AEDs or antiseizure).ti,ab. |
| 41. | benzodiazepine/ |
| 42. | piracetam/ |
| 43. | (Acetazolamide or Diamox or Eytazox or Carbamazepine or tegretol or Carbazepin or Clobazam or Frisium or Perizam or Tapclob or Zacco or Epitol or Finlepsin or Neurotol or Amizepine or Eslicarbazepine or Zebinix or Oxcarbazepine or Trileptal or Ethosuximide or emeside or zarontin or Lacosamide or vimpat or Lamotrigine or Lamictal or Levetiracetam or keppra or Desitrend or Nitrazepam or Mogadon or Perampanel or fycompa or Phenobarbital or Phenobarbitone or Primidone or mysoline or Liskantin or Phenytoin or Dilantin or epanutin or Retigabine or trobalt or Riluzole or Rilutek or Teglutik or Rufinamide or inovelon or Tiagabine or gabitril or Topiramate or topamax or sodium valproate or epilim or episenta or epival or valproic acid or convulex or depakote or Belvo or Syonell or vigabatrin or sabril* or "gamma vinyl gaba*" or "gamma vinyl gamma aminobutyric acid*" or Zonisamide or zonegran or Desizon or Benzodiazepine* or Clobazam or Clonazepam or rivotril or Diazepam or Diazemuls or Stesolid or Fosphenytoin or pro-epanutin or Lorazepam or Ativan or Midazolam or Hypnovel or Epistatus or buccolam or Phenobarbital or Phenytoin or Epanutin or Acetazolamide or diamox or Piracetam or nootropil).ti,ab. |
| 44. | exp beta adrenergic receptor blocking agent/ |
| 45. | ((b or beta*) adj3 (block* or antagonist*)).ti,ab. |
| 46. | (propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim or Beta-Prograne).ti,ab. |
| 47. | exp serotonin 3 antagonist/ |
| 48. | (5-HT3 adj2 Antagonis*).ti,ab. |
| 49. | ondansetron/ |
| 50. | (ondansetron or zofran or Dolasetron or Anzemet).ti,ab. |
| 51. | exp botulinum toxin/ |

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| 52. | (botulin* or onabotulinumtoxin* or abobotulinumtoxin* or incobotulinumtoxin* or prabotulinumtoxin* or rimabotulinum*).ti,ab. |
| 53. | (dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc or Azzalure or Bocouture or Myobloc or Jeuveau).ti,ab. |
| 54. | dantrolene/ |
| 55. | methocarbamol/ |
| 56. | tramadol/ |
| 57. | temazepam/ |
| 58. | flunitrazepam/ |
| 59. | flurazepam/ |
| 60. | nitrazepam/ |
| 61. | (dantrolene or dantrium or tizanidine or zanaflex or methocarbamol or robaxin or tramadol or Brimisol or Invodol or zamadol or zydol or larapam or mabron or marol or maxitram or tramquel or Tilodol or Tramulief or zeridame or tradorec or nitrazepam or temazepam or flunitrazepam or Flurazepam or dalmane or zaleplon or sonata or zolpidem or stilnoct or zoiclone or zimovane).ti,ab. |
| 62. | aminopyridine derivative/ |
| 63. | fampridine/ |
| 64. | (Fampyra or aminopyridine* or dalfampridine or fampridine* or pymadine or ampyra).ti,ab. |
| 65. | or/29-64 |
| 66. | 28 and 65 |
| 67. | gabapentin/ |
| 68. | (gabapentin* or 1-aminomethylcyclohexaneacetic acid or convalis or Neurontin).ti,ab. |
| 69. | or/67-68 |
| 70. | 28 and 69 |
| 71. | random*.ti,ab. |
| 72. | factorial*.ti,ab. |
| 73. | (crossover* or cross over*).ti,ab. |
| 74. | ((doubl* or singl*) adj blind*).ti,ab. |
| 75. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 76. | crossover procedure/ |
| 77. | single blind procedure/ |
| 78. | randomized controlled trial/ |
| 79. | double blind procedure/ |
| 80. | or/71-79 |
| 81. | systematic review/ |
| 82. | meta-analysis/ |
| 83. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 84. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 85. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 86. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 87. | (search* adj4 literature).ab. |
| 88. | (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. |
| 89. | cochrane.jw. |

| | |
|---|---|
| 90. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 91. | or/81-90 |
| 92. | 66 and (80 or 91) |
| 93. | 70 and (80 or 91) |
| 94. | 92 or 93 |

**Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Multiple Sclerosis] explode all trees |
| #2. | ((multiple or disseminated) NEAR/2 scleros*):ti,ab |
| #3. | (encephalomyelitis disseminata or disseminated encephalomyelitistis or ADEM):ti,ab |
| #4. | MS:ti |
| #5. | MeSH descriptor: [Myelitis, Transverse] this term only |
| #6. | transverse myelitis:ti,ab |
| #7. | (OR #1-#6) |
| #8. | MeSH descriptor: [gamma-Aminobutyric Acid] this term only |
| #9. | MeSH descriptor: [Baclofen] this term only |
| #10. | MeSH descriptor: [Pregabalin] this term only |
| #11. | ("4 aminobutanoic acid*" or "4 aminobutyric acid*" or "gamma aminobutyric acid*" or "hydrochloride gamma-aminobutyric*" or aminalon* or gammalon* or gaba or Baclofen* or baclophen* or "chlorophenyl NEAR gaba" or lioresal or pregabalin* or "3 isobutyl gaba" or "3-aminomethyl-5-methylhexanoic acid" or Alzain or Axalid or Lecaent or lyrica):ti,ab |
| #12. | MeSH descriptor: [Anti-Bacterial Agents] this term only |
| #13. | MeSH descriptor: [Antitubercular Agents] explode all trees |
| #14. | (antibacterial* or anti-bacterial* or antimycobacterial* or antitubercul* or anti-tubercul*):ti,ab |
| #15. | MeSH descriptor: [Isoniazid] explode all trees |
| #16. | (Isoniazid or Ftivazide or Isonex or Isonicotinic* or Phthivazid* or Tubazide or INH or Tebesium* or Cemidon):ti,ab |
| #17. | MeSH descriptor: [Anticonvulsants] explode all trees |
| #18. | (anti NEAR/2 (epileptic* or convulsant* or seizure*)):ti,ab |
| #19. | (antiepileptic* or anticonvulsant* or AEDs or antiseizure):ti,ab |
| #20. | MeSH descriptor: [Benzodiazepines] this term only |
| #21. | MeSH descriptor: [Midazolam] this term only |
| #22. | MeSH descriptor: [Piracetam] this term only |
| #23. | (Acetazolamide or Diamox or Eytazox or Carbamazepine or tegretol or Carbazepin or Clobazam or Frisium or Perizam or Tapclob or Zacco or Epitol or Finlepsin or Neurotol or Amizepine or Eslicarbazepine or Zebinix or Oxcarbazepine or Trileptal or Ethosuximide or emeside or zarontin or Lacosamide or vimpat or Lamotrigine or Lamictal or Levetiracetam or keppra or Desitrend or Nitrazepam or Mogadon or Perampanel or fycompa or Phenobarbital or Phenobarbitone or Primidone or mysoline or Liskantin or Phenytoin or Dilantin or epanutin or Retigabine or trobalt or Riluzole or Rilutek or Teglutik or Rufinamide or inovelon or Tiagabine or gabitril or Topiramate or topamax or sodium valproate or epilim or episenta or epival or valproic acid or convulex or depakote or Belvo or Syonell or vigabatrin or sabril* or "gamma vinyl gaba*" or "gamma vinyl gamma aminobutyric acid*" or Zonisamide or zonegran or Desizon or Benzodiazepine* or Clobazam or Clonazepam or rivotril or Diazepam or Diazemuls or Stesolid or Fosphenytoin or pro-epanutin or Lorazepam or Ativan or Midazolam or Hypnovel or Epistatus or buccolam or Phenobarbital or Phenytoin or Epanutin or Acetazolamide or diamox or Piracetam or nootropil):ti,ab |
| #24. | MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees |

| | |
|---|---|
| #25. | ((b or beta*) NEAR/3 (block* or antagonist*)):ti,ab |
| #26. | (propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim or Beta-Prograne):ti,ab |
| #27. | MeSH descriptor: [Serotonin 5-HT3 Receptor Antagonists] explode all trees |
| #28. | (5 HT3 NEAR/2 Antagonis*):ti,ab |
| #29. | MeSH descriptor: [Ondansetron] this term only |
| #30. | (ondansetron or zofran or Dolasetron or Anzemet):ti,ab |
| #31. | MeSH descriptor: [Botulinum Toxins] explode all trees |
| #32. | (botulin* or onabotulinumtoxin* or abobotulinumtoxin* or incobotulinumtoxin* or prabotulinumtoxin* or rimabotulinum*):ti,ab |
| #33. | (dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc or Azzalure or Bocouture or Myobloc or Jeuveau):ti,ab |
| #34. | MeSH descriptor: [Dantrolene] this term only |
| #35. | MeSH descriptor: [Methocarbamol] this term only |
| #36. | MeSH descriptor: [Tramadol] this term only |
| #37. | MeSH descriptor: [Temazepam] this term only |
| #38. | MeSH descriptor: [Flunitrazepam] this term only |
| #39. | MeSH descriptor: [Flurazepam] this term only |
| #40. | MeSH descriptor: [Nitrazepam] this term only |
| #41. | (dantrolene or dantrium or tizanidine or zanaflex or methocarbamol or robaxin or tramadol or Brimisol or Invodol or zamadol or zydol or larapam or mabron or marol or maxitram or tramquel or Tilodol or Tramulief or zeridame or tradorec or nitrazepam or temazepam or flunitrazepam or Flurazepam or dalmane or zaleplon or sonata or zolpidem or stilnoct or zoiclone or zimovane):ti,ab |
| #42. | MeSH descriptor: [Aminopyridines] this term only |
| #43. | MeSH descriptor: [4-Aminopyridine] this term only |
| #44. | (Fampyra or Aminopyridine* or dalfampridine or fampridine* or pymadine or ampyra):ti,ab |
| #45. | (OR #8-#44) |
| #46. | #7 AND #45 |
| #47. | MeSH descriptor: [Gabapentin] this term only |
| #48. | (gabapentin* or 1 aminomethylcyclohexaneacetic acid or convalis or Neurontin):ti,ab |
| #49. | (OR #47-#48) |
| #50. | #7 AND #49 |
| #51. | conference:pt or (clinicaltrials or trialsearch):so |
| #52. | #46 or #50 |
| #53. | #52 NOT #51 |

**Epistemonikos search terms**

| | |
|---|---|
| 1. | (((title:(multiple sclerosis) OR abstract:(multiple sclerosis)) AND (title:(ataxia OR tremor) OR abstract:(ataxia OR tremor))) |
| 2. | (((advanced_title_en:("multiple sclerosis" OR "disseminated sclerosis" OR "encephalomyelitis disseminata" OR MS OR "transverse myelitis") OR advanced_abstract_en:("multiple sclerosis" OR "disseminated sclerosis" OR "encephalomyelitis disseminata" OR MS OR "transverse myelitis")) AND ((advanced_title_en:(gabapentin* OR 1-aminomethylcyclohexaneacetic acid OR |

| | |
|---|---|
| | convalis OR Neurontin) OR advanced_abstract_en:(gabapentin* OR 1-aminomethylcyclohexaneacetic acid OR convalis OR Neurontin))) |
| 3. | 1 or 2 |

## 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 7: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 01 January 2014 – 07 September 2021 | Health economics studies<br>Quality of life studies<br><br>Exclusions (animal studies, letters, comments, children) |
| Embase | 01 January 2014 – 07 September 2021 | Health economics studies<br>Quality of life studies<br><br>Exclusions (animal studies, letters, comments, conference abstracts, children) |
| Centre for Research and Dissemination (CRD) | HTA – 01 January 2014 – 31 March 2018<br>NHSEED – 01 January 2014 – March 2015 | None |
| The International Network of Agencies for Health Technology Assessment (INAHTA) | 01 January 2018 – 07 September 2021 | None |

**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 |

**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 |

**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 |

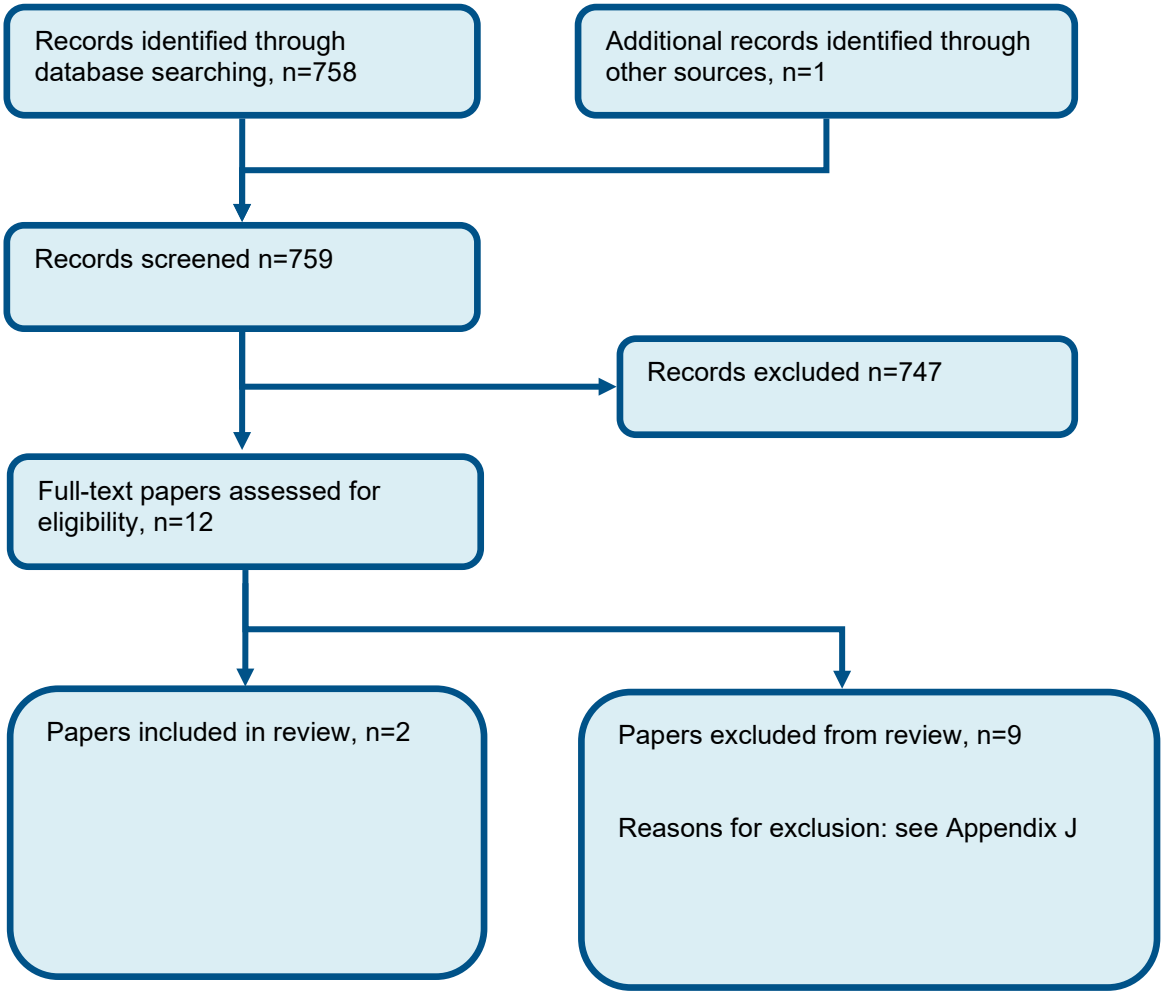
**INAHTA search terms**

| | |
|---|---|
| 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)) |

# Appendix C – Effectiveness evidence study selection

**Figure 1: Flow chart of clinical study selection for the review of pharmacological management of ataxia and tremor in MS**



# Appendix D – Effectiveness evidence

## D.1 Study extracted using EPPI reviewer (new study identified in current update)

### Boonstra, 2020

**Bibliographic Reference** Boonstra, F. M. C.; Evans, A.; Noffs, G.; Perera, T.; Jokubaitis, V.; Stankovich, J.; Vogel, A. P.; Moffat, B. A.; Butzkueven, H.; Kolbe, S. C.; van der Walt, A.; OnabotulinumtoxinA treatment for MS-tremor modifies fMRI tremor response in central sensory-motor integration areas; Multiple Sclerosis and Related Disorders; 2020; vol. 40; 101984

#### Study details

| | |
|---|---|
| **Secondary publication of another included study- see primary study for details** | No |
| **Other publications associated with this study included in review** | No. This is an extension of a cross-sectional study (not included in our review). |
| **Trial name / registration number** | ACTRN12617000379314. Trial name not reported. |
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Australia |
| **Study setting** | Hospital |

| | |
|---|---|
| **Study dates** | Recruitment was between March 2016 and April 2018. |
| **Sources of funding** | Funded by NHMRC Project Grant (1085461 CIA Van der Walt) and Fellowship (1135683 Vogel). |
| **Inclusion criteria** | People with relapsing-remitting and secondary-progressive multiple sclerosis and unilateral upper limb tremor. |
| **Exclusion criteria** | Treatment with BoNT-A in the 6 months prior to recruitment, contraindication to BoNT-A injections, inability to cease other anti-tremor medications at least 1 week before baseline, or upper limb weakness (strength less than 4.5/5). |
| **Recruitment / selection of participants** | 43 participants with relapsing-remitting and secondary-progressive multiple sclerosis and unilateral upper limb tremor were recruited between March 2016 and April 2018. |
| **Intervention(s)** | An expert movement disorder neurologist administered targeted injections of BoNT-A (Botox; Alergan Australia Inc) after a careful assessment of the tremor pattern. A maximum dose of 150 IU BoNT-A was injected at the baseline visit.<br><br>An unblinded pharmacist prepared in equal volumes 100 units of BoNT-A diluted per 2mL 0.9% sterile saline or 2mL 0.9% sterile saline syringes. To optimise targeted treatment, injections were guided using the Dantec Clavis handheld electromyogram (EMG) and stimulation device (Natus Neurology). |
| **Population subgroups** | Not reported. |
| **Comparator** | An expert movement disorder neurologist administered targeted injection of placebo after a careful assessment of the tremor pattern. A maximum dose of 150 IU normal saline placebo was injected at the baseline visit. |
| **Number of participants** | 43 (n=21, BoNT-A; n=22 placebo) |
| **Duration of follow-up** | 12 weeks |
| **Indirectness** | No |

| | |
|---|---|
| **Additional comments** | Intention to treat |

## Study arms

### OnabotulinumtoxinA (BoNT-A) (N = 21)

| | |
|---|---|
| **Indirectness** | No |

### Placebo (N = 22)

| | |
|---|---|
| **Indirectness** | No |

## Characteristics

### Arm-level characteristics

| Characteristic | OnabotulinumtoxinA (BoNT-A) (N = 21) | Placebo (N = 22) |
|---|---|---|
| **% Female**<br><br>Nominal | 71.4 | 77.3 |
| **Mean age (SD)**<br><br>Mean (SD) | 45.9 (13.5) | 47 (9.35) |
| **Disease duration** years (SD)<br><br>Mean (SD) | 11.1 (7.55) | 16.6 (7.1) |
| **Tremor duration** years (sd)<br><br>Mean (SD) | 7.05 (8.1) | 9.95 (7.58) |

| Characteristic | OnabotulinumtoxinA (BoNT-A) (N = 21) | Placebo (N = 22) |
|---|---|---|
| **Disease course**<br>relapsing remitting (%)<br><br>Custom value | 42.9% | 31.8% |
| **Disease course**<br>secondary progressive MS (%)<br><br>Custom value | 52.4% | 68.2% |
| **Disease course**<br>Primary progressive MS (%)<br><br>Custom value | 4.8% | 0% |
| **EDSS**<br><br>Mean (SD) | 4.41 (1.76) | 3.95 (1.71) |

## Outcomes

### Study timepoints

- 12 week

### BoNT-A compared to placebo at 12 weeks

| Outcome | 12 week, OnabotulinumtoxinA (BoNT-A), N = 21 | 12 week, Placebo, N = 22 |
|---|---|---|
| **Tremor severity**<br>using Bain score<br><br>Mean (SD) | -0.79 (1.13) | -0.6 (1.31) |

| Outcome | 12 week, OnabotulinumtoxinA (BoNT-A), N = 21 | 12 week, Placebo, N = 22 |
|---|---|---|
| **Handwriting**<br><br>Mean (SD) | -0.53 (0.84) | -0.25 (1.21) |
| **Archimedes**<br><br>Mean (SD) | -0.63 (1.42) | -0.25 (1.33) |

Tremor severity - Polarity - Lower values are better
Handwriting - Polarity - Lower values are better
Archimedes - Polarity - Lower values are better
Tremor measurement: Tremor was recorded at rest, posture against gravity, in the bat-wing position and with finger-nose-testing. Tremor was rated using the Bain score (where 0=no tremor and 10=severe tremor) for overall severity, writing a standardised sentence ("This is a sample of my best handwriting") and Archimedes spiral drawing on a pre-drawn pattern.

**Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**
**Tremor severity_12 weeks**

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |

| Section | Question | Answer |
|---|---|---|
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High |
| Overall bias and Directness | Overall Directness | Directly applicable |

**Handwriting_12 weeks**

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High |
| Overall bias and Directness | Overall Directness | Directly applicable |

**Archimedes_12 weeks**

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High |
| Overall bias and Directness | Overall Directness | Directly applicable |

## D.2 Studies extracted in previous review version

<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>Source of funding</th></tr>
<tr>
<td>Van Der Walt et al. A double-blind, randomised, controlled study of botulinum toxin type A in MS-related tremor. Neurology 2012; 79:92-99</td>
<td>Randomised double blind cross-over trial.<br><br>Randomisation was not per person but per affected arm (though this would have been the same as per person for those affected unilaterally). When bilateral tremor was present both limbs were randomised separately.<br><br>No details of randomisation or allocation concealment, though not crucial for a cross-over.</td>
<td>25 people randomised (36 limbs as 10 people were bilateral). 19 limbs allocated to BT first – 2 excluded from analysis due to relapse (1) and pseudo relapse (1) during trial. Relapses happened during BT injection phase. 17 limbs allocated to placebo first – 1 excluded from analysis after discontinuing intervention (which one is not clear but appears to be placebo) due to painful injections.<br><br>33 limbs involved in final analysis. Attrition small and probably not related to outcome, so no attrition bias assumed.</td>
<td>Inclusion: patients with RR and SP MS with disabling arm tremor.<br><br>Exclusion: treatment with botulinum toxin in past 6 months; parkinsonism; essential tremor; inability to cease anti-tremor medications; <80% upper limb strength.
<table>
<tr><th>Baseline characteristic</th><th>Value</th></tr>
<tr><td>age</td><td>49.6(11)</td></tr>
<tr><td>Female sex</td><td>17/23</td></tr>
<tr><td>RRMS<br>SPMS</td><td>6/23<br>17/23</td></tr>
<tr><td>Disease duration</td><td>17(8.5)</td></tr>
<tr><td>Tremor duration</td><td>6.5(5.1)</td></tr>
<tr><td>EDSS</td><td>5.5(4-6.5)</td></tr>
<tr><td>Ataxia score</td><td>18.5(10.3-29.3)</td></tr>
<tr><td>Bain composite tremor score</td><td>5(3-7.5)</td></tr>
</table>
</td>
<td>Maximum dose of 100IU botulinum toxin injected at baseline. Injections targeted at agonist and antagonist muscles involved in the tremor pattern. Treatment given under EMG guidance.<br><br>Cross-over.</td>
<td>Same dose of identical placebo injected at baseline. Injections targeted at agonist and antagonist muscles involved in the tremor pattern. Treatment given under EMG guidance.<br><br>Cross-over.</td>
<td>3 months</td>
<td>Academic /clinical only.</td>
</tr>
</table>

| Reference | Study type | No. pts | Patient characteristics | | Intervention | Comparison | Length of follow-up | Source of funding |
|---|---|---|---|---|---|---|---|---|
| | Outcome assessor blinding reported. An identical placebo used so presumably patients were blinded, though not reported. Unclear if HCPs were blinded. Described as 'double blind' so possible that only patients and not HCPs were blinded. | | (0-10). Higher worse | | | | | |
| | | | Bain writing score (0-10). Higher worse | 3(1-9) | | | | |
| | | | Bain Archimedes spiral (0-10).Higher worse | 3(1-8) | | | | |
| | | | | | | | | |

| **Results: Article used non-parametric analyses. n=33 unless stated** | | | | |
|---|---|---|---|---|
| | **Median (IQR) change from baseline for Botulinum toxin (whole cross-over cohort)** | **Median (IQR) change from baseline for placebo (whole cross-over cohort)** | **Wilcoxon signed ranks test p** | |

| Reference | Study type | No. pts | Patient characteristics | Intervention | Comparison | Length of follow-up | Source of funding |
|---|---|---|---|---|---|---|---|
| **Bain Tremor scores (changes from baseline to 12 weeks)** | | | | | | | |
| Bain composite tremor score (0-10). Higher worse | -2(-2 to -1) | 0(-1 to 1) | 0.0001 | | | | |
| Bain writing score (0-10). Higher worse. N=22 | -1(-1 to 0) | 0(0 to 0) | 0.002 | | | | |
| Bain Archimedes spiral (0-10). Higher worse. N=22 | -1(-2 to 0) | 0(0 to 1) | 0.0007 | | | | |
| **Writing, drawing and functional task scores (changes from baseline to 12 weeks)** | | | | | | | |
| CRST writing (0-4) Higher worse. N=22 | 0(-1 to 0) | 0(0 to 0) | 0.197 | | | | |
| CRST drawing (0-4) Higher worse. N=22 | -0.5(-1 to 0) | 0(0 to 0) | 0.024 | | | | |
| ICARS Archimedes spiral (0-4). Higher worse. N=22 | 0(-1 to 0) | 0(0 to 0) | 0.3351 | | | | |
| CRST pouring (0-4) Higher worse. N=29 | 0(-1 to 0) | 0(0 to 0) | 0.0628 | | | | |
| Drinking from cup (0-4) Higher worse. N=29 | 0(-1 to 0) | 0(0 to 0) | 0.0089 | | | | |
| 9 hole peg test. N=28 | -4.5(-14 to -1) | 0(-6 to 4) | 0.0195 | | | | |

| Reference | Study type | No. pts | Patient characteristics | Intervention | Comparison | Length of follow-up | Source of funding |
|---|---|---|---|---|---|---|---|
| **Kinetic tremor scores (changes from baseline to 12 weeks)** | | | | | | | |
| Kinetic tremor severity(0-4) Higher worse. | -1(-1 to 0) | 0(0 to 1) | <0.0001 | | | | |
| CRST action tremor arm (0-4). Higher worse | 0(-1 to 0) | 0(0 to 0) | 0.021 | | | | |
| CRST action tremor amplitude (cm). Higher worse | -1(-2 to 0) | 0(0 to 0.5) | 0.0012 | | | | |
| ICARS finger-finger test. Higher worse. | 0(-1 to 0) | 0(0 to 0) | 0.4274 | | | | |
| **Postural tremor scores (changes from baseline to 12 weeks)** | | | | | | | |
| Postural tremor severity (0-4). Higher worse. | -1(-1 to 0) | 0(0 to 0) | 0.0161 | | | | |
| Batwing position tremor (0-4). Higher worse. | -1(-1 to 0) | 0(0 to 0) | 0.0268 | | | | |
| CRST postural tremor arm (0-4). Higher worse | 0(-1 to 0) | 0(0 to 0) | 0.0076 | | | | |

| Reference | Study type | No. pts | Patient characteristics | Intervention | Comparison | Length of follow-up | Source of funding |
|---|---|---|---|---|---|---|---|
| CRST postural tremor amplitude (cm). Higher worse | -0.5(-5 to 0) | 0(0 to 0.5) | 0.0077 | | | | |
| **Adverse events** | | | | | | | |
| Muscle weakness | 14/33 | 2/33 | 0.0005 | | | | |
| **Ataxia (changes from baseline to 12 weeks)** | | | | | | | |
| SARA score change from baseline. Higher worse | -2(-3 to 0) | 0.5(1.5 to 2) | 0.089 | | | | |
| **Quality of life (changes from baseline to 12 weeks)** | | | | | | | |
| QUEST score. Higher is worse | 0(-4 to 6) | -4(-12 to 1) | 0.1136 | | | | |
| **Risk of bias** | | | | | | | |
| All outcomes from this study were downgraded 1 increment for risk of bias. Footnotes provided in modified GRADE tables explain that this was due to attrition bias. | | | | | | | |

# Appendix E - Forest plots

## E.1 BoNT-A (Botox) versus Placebo (Follow-up at 12 weeks)

**Figure 2: Tremor severity (Bain score, 0-1) (lower is better)**

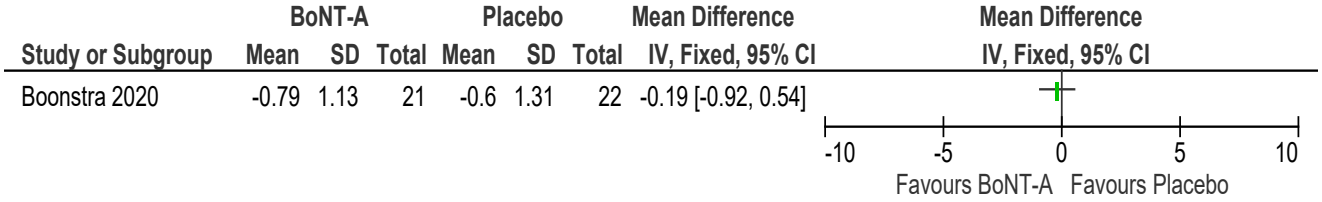



**Figure 3: Handwriting (lower is better)**

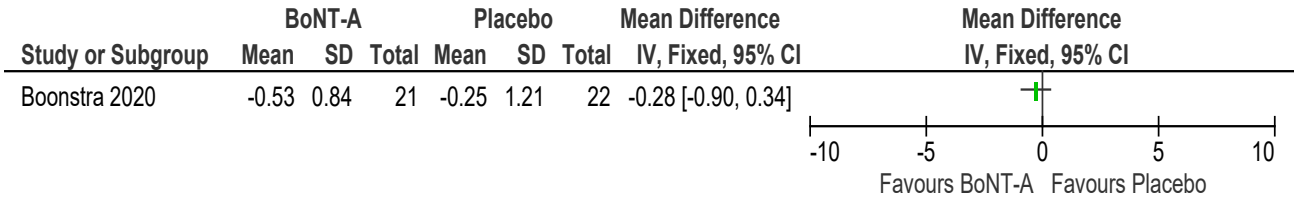
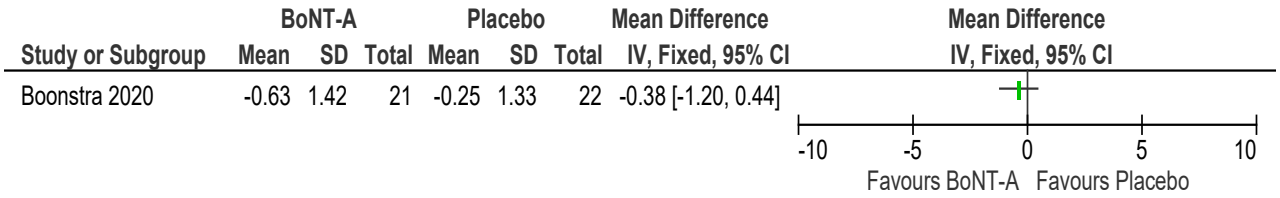


**Figure 4: Archimedes spiral (lower is better)**



# Appendix F – GRADE tables

### Table 8: Clinical evidence profile: BoNT-A (Botox) versus placebo (new study identified in current update)

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | pharmacological interventions | compared to each other or usual care | Relative (95% CI) | Absolute (95% CI) | | |
| **Tremor severity (Bain score, 0 to 10) (follow up: 12 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | serious [b] | none | 21 | 22 | - | MD **0.19 lower** (0.92 lower to 0.54 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| **Handwriting (writing a standardised sentence)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | serious [c] | none | 21 | 22 | - | MD **0.28 lower** (0.9 lower to 0.34 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| **Archimedes spiral drawing on a pre-drawn pattern** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | serious [d] | none | 21 | 22 | - | MD **0.38 lower** (1.2 lower to 0.44 higher) | ⨁⨁◯◯ LOW | CRITICAL |

a. Downgraded by 1 increment due to concerns about high risk of bias in the randomisation process.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group SD for % baseline change by 0.5 and were ±0.65

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group SD for % baseline change by 0.5 and were ±0.60

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MIDs calculated by multiplying the control group SD for % baseline change by 0.5 and were ±0.66

### Table 9: Clinical evidence profile: Botulinum versus placebo (study included in previous version of the guideline )

The evidence was reported as medians and IQR and therefore could not be analysed in GRADE. It is therefore summarised in a modified GRADE table.

| Quality assessment | | | | | | | Median (IQR) change from baseline | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Botulinum Toxin A | Placebo | P value for Wilcoxon signed ranks | Absolute | | |
| **Quality of Life QUEST score. Higher better** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | Serious imprecision[B] | None | 0(-4 to 6) | -4(-12 to 1) | 0.1136 | NA | LOW | CRITICAL |
| **Impact on carers** | | | | | | | | | | | | |
| No data available | | | | | | | | | | | | |
| **Bain composite tremor score (0-10). Higher worse** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -2(-2 to -1) | 0(-1 to 1) | 0.0001 | NA | MODERATE | CRITICAL |
| **Bain writing score (0-10). Higher worse. N=22** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -1(-1 to 0) | 0(0 to 0) | 0.002 | NA | MODERATE | CRITICAL |
| **Bain Archimedes spiral (0-10). Higher worse. N=22** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -1(-2 to 0) | 0(0 to 1) | 0.0007 | NA | MODERATE | CRITICAL |
| **CRST writing (0-4) Higher worse. N=22** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | Serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.197 | NA | LOW | CRITICAL |
| **CRST drawing (0-4) Higher worse. N=22** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -0.5(-1 to 0) | 0(0 to 0) | 0.024 | NA | MODERATE | CRITICAL |
| **ICARS Archimedes spiral (0-4). Higher worse. N=22** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | Serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.3351 | NA | LOW | CRITICAL |
| **CRST pouring (0-4) Higher worse. N=29** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | Serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.0628 | NA | LOW | CRITICAL |
| **Drinking from cup (0-4) Higher worse. N=29** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.0089 | NA | MODERATE | CRITICAL |
| **9-hole peg test. N=28** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -4.5(-14 to -1) | 0(-6 to 4) | 0.0195 | NA | MODERATE | CRITICAL |
| **Kinetic tremor severity(0-4) Higher worse.** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -1(-1 to 0) | 0(0 to 1) | <0.0001 | NA | MODERATE | CRITICAL |
| **CRST action tremor arm (0-4). Higher worse** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.021 | NA | MODERATE | CRITICAL |
| **CRST action tremor amplitude (cm). Higher worse** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -1(-2 to 0) | 0(0 to 0.5) | 0.0012 | NA | MODERATE | CRITICAL |
| **ICARS finger-finger test. Higher worse.** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | Serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.4274 | NA | LOW | CRITICAL |
| **Postural tremor severity (0-4). Higher worse.** | | | | | | | | | | | | |

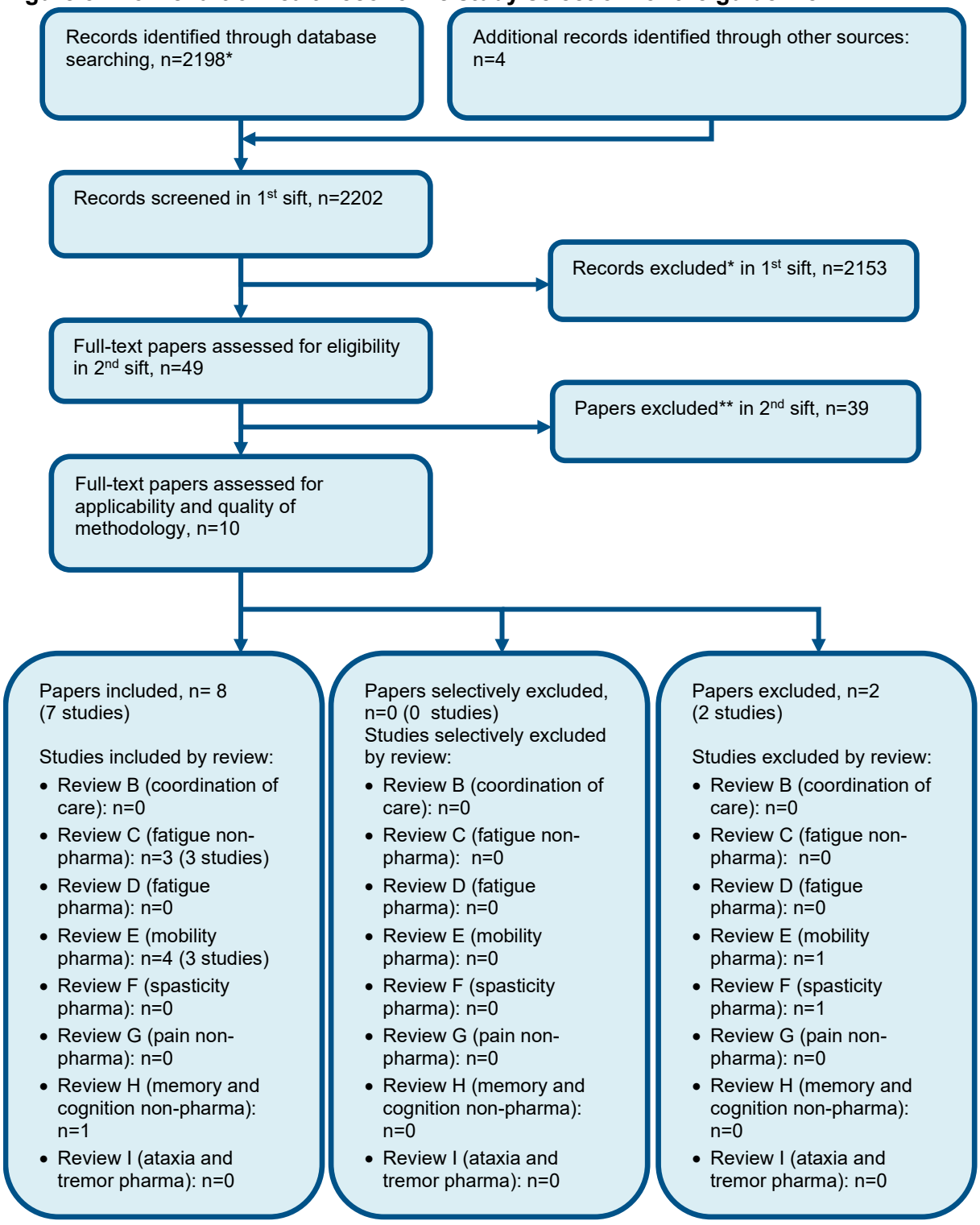
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -1(-1 to 0) | 0(0 to 0) | 0.0161 | NA | MODERATE | CRITICAL |
| **Batwing position tremor (0-4). Higher worse.** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -1(-1 to 0) | 0(0 to 0) | 0.0268 | NA | MODERATE | CRITICAL |
| **CRST postural tremor arm (0-4). Higher worse** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | 0(-1 to 0) | 0(0 to 0) | 0.0076 | NA | MODERATE | CRITICAL |
| **CRST postural tremor amplitude (cm). Higher worse** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[B] | None | -0.5(-5 to 0) | 0(0 to 0.5) | 0.0077 | NA | MODERATE | CRITICAL |
| **Ataxia rating scores - SARA score change from baseline. Higher worse** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | Serious imprecision[B] | None | -2(-3 to 0) | 0.5(1.5 to 2) | 0.089 | NA | LOW | CRITICAL |
| **Adverse events - Muscle weakness** | | | | | | | | | | | | |
| 1<br>Van Der Walt 2012A | Cross-over RCT | Serious risk of bias[A] | No serious inconsistency | No serious indirectness | No serious imprecision[C] | None | 14/33<br>(42.4%) | 2/33 (6.1%) | RR: 7 (1.72 to 28.41) | 364 more per 1000 (from 44 more to 1000 more) | MODERATE | CRITICAL |

[A] The outcome was downgraded by one increment because the study had attrition bias.
[B] Because of the lack of confidence intervals or absolute effect sizes, imprecision was based on the Wilcoxon signed ranks test. If $p \leq 0.05$ it was rated as precise and if $p > 0.05$ as seriously imprecise.
[C] This outcome was rated as precise because neither confidence interval crossed either of the default MIDs (0.80 and 1.25)

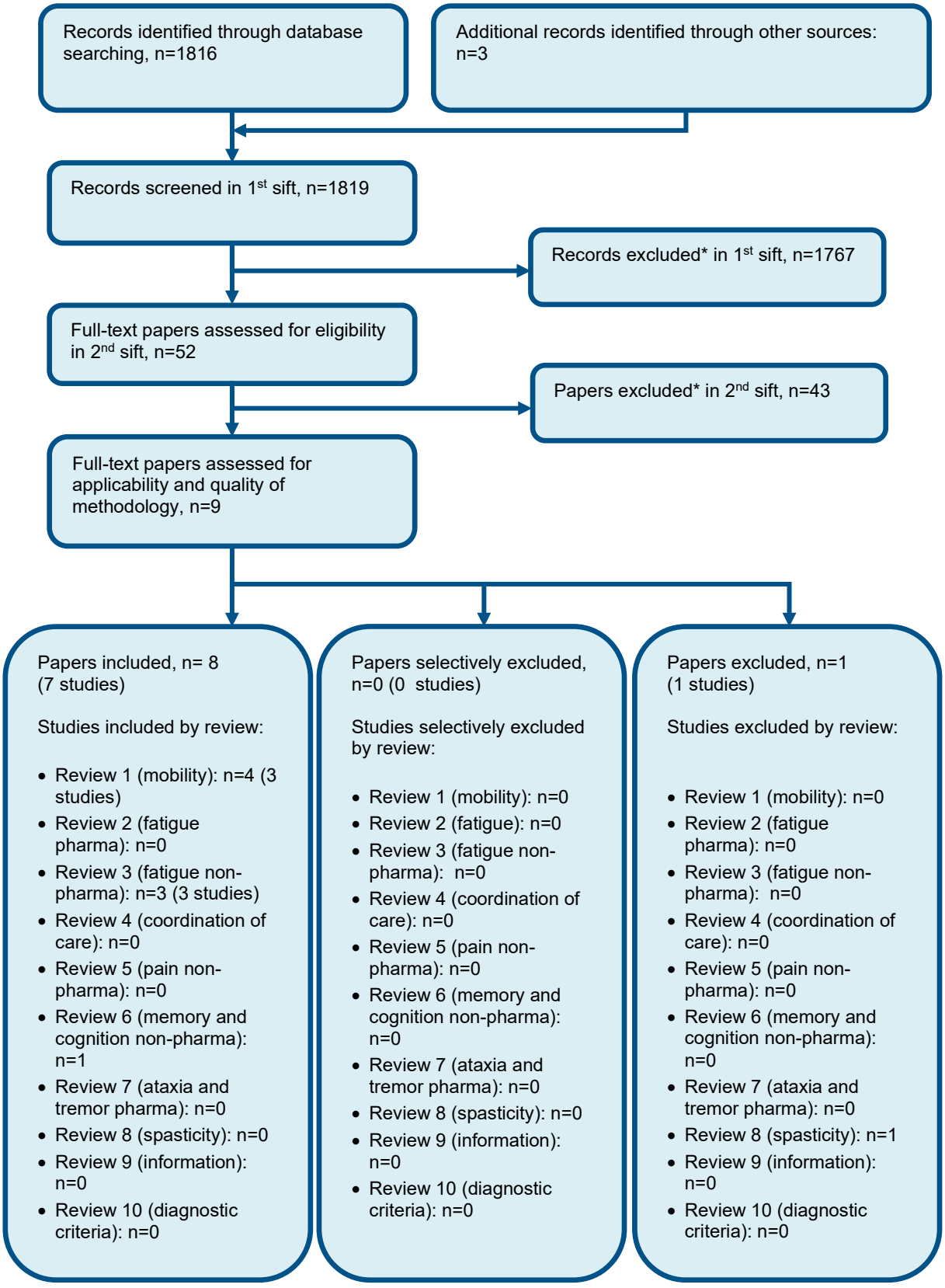
# Appendix G – Economic evidence study selection

**Figure 5: Flow chart of health economic study selection for the guideline**




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

**Figure 6: Flow chart of health economic study selection for the guideline**




* Non-relevant population, intervention, comparison, design or setting; non-English language

# Appendix H – Economic evidence tables

None.

# Appendix I – Health economic model

No original economic modelling was undertaken.

# Appendix J – Excluded studies

## Clinical studies

### Table 10: Studies excluded from the clinical review

| Study | Code [Reason] |
|---|---|
| Applebee, A., Goodman, A. D., Mayadev, A. S. et al. (2015) Effects of Dalfampridine Extended-release Tablets on 6-minute Walk Distance in Patients With Multiple Sclerosis: A Post Hoc Analysis of a Double-blind, Placebo-controlled Trial. Clinical Therapeutics 37(12): 2780-7 | - Study does not include outcomes relevant to this review |
| Fasano, A. and Deuschl, G. (2015) Therapeutic advances in tremor. Movement Disorders 30(11): 1557-65 | - Review article but not a systematic review |
| Mittal, S. O.; Lenka, A.; Jankovic, J. (2019) Botulinum toxin for the treatment of tremor. Parkinsonism & Related Disorders 63: 31-41 | - Study design not relevant to this review protocol<br>*Longitudinal study* |
| Nicholas, R. and Chataway, J. (2007) Multiple sclerosis. Clinical Evidence 15: 15 | - Duplicate reference<br>*Older version of a report that was updated in 2012 – the 2012 references of the same title is available on EPPI* |
| Nicholas, R. and Chataway, J. (2009) Multiple sclerosis. Clinical Evidence 14: 14 | - Duplicate reference<br>*Older version of a report that was updated in 2012 – the 2012 references of the same title is available on EPPI* |
| Nicholas, R. and Rashid, W. (2012) Multiple sclerosis. Clinical Evidence 10: 10 | - Systematic review used as source of primary studies |
| Olson, W. H.; Gruenthal, M.; Olson, W. L. (1997) Efficacy of gabapentin for relief of upper motor symptoms in patients with multiple sclerosis. Multiple sclerosis:3suppl: 215 | - Study does not include outcomes relevant to this review<br>*Gabapentin in the treatment of spasticity and painful muscle spasms not ataxia and tremor. The outcome measures were Visual Faces Scale rating, Kurtzke Disability Scale, quantitative surface electromyography, Ashworth Scale, presence or absence of clonus in response to rapid ankle dorsiflexion and wrist extension, presence or absence of reflex withdrawal in response to nailbed pressure to the first finger, and assessment of Babinski response.* |

| Study | Code [Reason] |
|---|---|
| Stolyarov, I. D.; Petrov, A. M.; Boyko, A. N. (2020) Efficacy and safety of Kinezia (fampridine) in the complex therapy of multiple sclerosis. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova 120(11): 45-52 | - Study not reported in English |
| Zesiewicz, T. A., Wilmot, G., Kuo, S. H. et al. (2018) Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 90(10): 464-471 | - Systematic review used as source of primary studies<br><br>*This include pharma and non-pharma interventions. Looked at all the included studies on MS. Some are non-pharma which are outside the scope of this guideline. The study on pharma treatment of MS is on dolasetron mesylate which is a serotonin receptor antagonist and not included as an intervention in this question. The study is Monaca-Charley C, Stojkovic T, Duhamel A, De Seze J, Ferriby D, Vermersch P. Double-blind crossover study with dolasetron mesilate, a 5-HT3 receptor antagonist in cerebellar syndrome secondary to multiple sclerosis. J Neurol 2003;250: 1190–1194* |
| Zheng, X., Wei, W., Liu, P. et al. (2020) Botulinum toxin type A for hand tremor: a meta-analysis of randomised controlled trials. Neurologia i Neurochirurgia Polska 54(6): 561-567 | - Systematic review used as source of primary studies<br><br>*Checked relevant studies.Van Der Walt 2012 already included in CG 186. Boonstra 2020 on order.* |

## 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 11: Studies excluded from the health economic review**

| Reference | Reason for exclusion |
|---|---|
| None | |

# Appendix K – Research recommendations – full details

## K.1 Research recommendation

For adults with MS, what is the clinical and cost effectiveness of pharmacological interventions for ataxia and tremor?

### K.1.1 Why this is important

Ataxia is a common and distressing symptom in MS and can vary from a mild arm tremor to whole-body movements that are so severely uncoordinated that it is impossible for people to carry out activities of daily living independently. It can affect any part of the body including upper limbs, head and trunk and lower limbs as well as the coordination of eye movements, speech, swallowing and breathing. Therapy interventions focus on helping people to relearn movement strategies and improve strength in order to improve their coordination and teaching people compensatory strategies to allow them to continue functioning at a maximal level. These interventions, however, have not been adequately researched.

### K.1.2 Rationale for research recommendation

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| Importance to 'patients' or the population | If pharmacological interventions for ataxia and tremor are shown to offer clinically important benefits to the management of ataxia and tremor for people with MS, at a reasonable cost threshold, then it may be an important modality to improve current practice and enhance clinical outcomes in this patient group.<br>If specific interventions are identified to be effective, this can support people with MS to choose effective interventions while an increased understanding of optimal strategies can help standardise care and improve patient outcomes. |
| Relevance to NICE guidance | This research can reduce the existing uncertainty regarding the clinical and cost-effectiveness of pharmacological interventions for ataxia and tremor and support decision making in the development of future recommendations. |
| Relevance to the NHS | A clear recommendation for pharmacological interventions for ataxia and tremor will offer clinicians clearer guidance on best care for people with MS. Increased knowledge of pharmacological interventions would improve and standardise care. |
| National priorities | The national service framework for long term conditions supports the early management of symptoms |
| Current evidence base | Two RCTs comparing Botulinum toxin type A with placebo were included in the evidence review both with a sample size < 50. No RCTs were identified for any of the other interventions specified in the protocol. |

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| Equality considerations | Trials are unlikely to impact on equality issues. |

### K.1.3 Modified PICO table

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|---|---|
| Population | <u>Inclusion:</u><br>Adults (≥18 years) with MS, including people receiving palliative care.<br><br><u>Exclusion:</u><br>Children and young people (≤18 years). |
| Intervention | Pharmacological interventions:<br>• Baclofen (oral/intrathecal)<br>• Isoniazid<br>• Antiepileptics for example Carbamazepine<br>• beta blockers for example Propranolol<br>• benzodiazepines for example Clonazepam<br>• Primidone<br>• Ondansetron<br>• Fampridine<br>• Botulinum toxin<br>• Gabapentin<br>• Or combinations of the above |
| Comparator | Interventions will be compared to each other (both within and between classes), placebo/sham, or usual care with no pharmacological treatment. |
| Outcome | • Health-related Quality of Life (validated), for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale.<br>• Ataxia measurement scales:<br>  ○ International Cooperative Ataxia Rating Scale (ICARS)<br>• Tremor rating scales (TRS),<br>  ○ Fahn<br>  ○ SARA<br>  ○ 9-hole peg test<br>  ○ Archimedean Spiral<br>• 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) or + mobility scales<br>• Adverse effects of treatment:<br>• Withdrawal due to adverse effects (e.g., fatigue)<br>• Patient-reported outcomes, for example symptoms of ataxia and tremor or adverse events.<br>• Impact on carers.<br><br>Follow-up:<br>- At 6 months (if multiple time points are reported, we will only record the closest reported time point up to 6 months)<br>• >6 months - 12 months (data from >1 year follow up may be included but will be downgraded) |
| Study design | RCT |
| Timeframe | Medium term |
| Additional information | None |