National Institute for Health and Care Excellence

Final

Multiple sclerosis in adults: management

[D] Evidence review for the pharmacological management of fatigue

NICE guideline NG220

Evidence reviews underpinning recommendations 1.5.12 to 1.5.16 and research recommendations in the NICE guideline

June 2022

Final

These evidence reviews were developed by the Guideline Development Team NGC

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-4607-5

Contents

1 Pharmacological management of fatigue

1.1 Review question

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

1.1.1 Introduction

Fatigue is thought to be the commonest and one of the most debilitating symptoms of multiple sclerosis. It can affect up to 80% of the MS population. Causes can be multifactorial with both physical and cognitive implications. There are recognised associations with heat, overexertion, stress or maybe the time of the day. The symptoms appear completely out of proportion to prior activity levels.

Fatigue is a universal experience; it is a self-recognised phenomenon that is subjective in nature. It is a common symptom in the general population and can be caused by a variety of medical problems such as anaemia or thyroid disease. Amantadine is available to treat fatigue in people with MS – but the mechanism of action, risks or benefits are unclear and have not been quantified. If trialled, medication such as amantadine found to directly help fatigue only benefits a proportion of MS sufferers and does not always eliminate the problem altogether. In addition to fatigue being a primary symptom of MS, some medication to control other MS symptoms may cause drowsiness and exacerbate underlying fatigue further.

There is no clear pharmacological management and therefore possible disparity in practice. New treatments may be available to help treat and manage fatigue in MS.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care, who are experiencing fatigue. Exclusion: Children and young people (≤18 years).
Interventions	• Amantadine • SSRIs • Aspirin specifically before exercise • Modafinil • Combinations of the above
Comparisons	Interventions will be compared to each other (both within and between classes), placebo/sham, or usual care.
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical. • Patient-reported outcome measures to assess MS fatigue, including MFIS Fatigue Severity Scale (FSS), National Fatigue Index (NFI), MS-specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS), • Visual Analogue Scale (VAS) for fatigue • Adverse effects of treatment.

	○ Adverse events leading to withdrawal ○ Disruption of sleep ○ cardiac events/arrhythmias • Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale. • Impact on patients/carers. • Cognitive functions, such as memory and concentration • Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments. • Epworth sleepiness scale **Follow up:** • 3-6 months (minimum of 3 months but can include 1-3 months and downgrade) • >6 months – 1 year (data from >1 year follow up may be included but will be downgraded)
Study design	Systematic reviews of RCTs and RCTs Crossover RCTs with a washout period of at least 1 week will be included

For full details see the review protocol in Appendix A.

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

Seventeen randomised controlled trial studies (from twenty-one papers) were included in the review;[1, 2, 4, 7-10, 12-16, 19, 22, 24-26] these are summarised in Table 2 below. These studies included 12 parallel trials;[2, 4, 7, 9, 10, 12-15, 22, 24, 26] and 5 crossover trials[1, 8, 16, 19, 25]. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

These studies include the following comparisons:

- Amantadine compared to aspirin[25]
- Amantadine compared to modafinil[14, 19]
- Amantadine compared to placebo[1, 2, 8, 13, 14, 16, 19, 22]
- SSRIs compared to placebo (analysed as a class, the formulations included are):
  - Fluoxetine compared to placebo[4, 7]
  - Paroxetine compares to placebo[9]
- Aspirin compared to placebo[24]
- Modafinil compared to placebo[10, 14, 15, 19, 26]
- Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine[12]

No relevant clinical studies comparing any intervention with usual care were identified. There was limited evidence comparing active treatments to each other and comparing combinations of treatments to other treatments and placebo. No studies reported the following outcomes:

- Visual Analogue Scale (VAS) measure of fatigue
- Impact on patients/carers

All studies used oral preparations and conventional doses of the study medication. The majority of outcomes were reported at less than 3 months. These outcomes were included in the review but downgraded for outcome indirectness as they did not fulfil a period of 3-6 months as stated in the protocol (see indirectness section for further information).

Inconsistency

Two outcomes had significant statistical heterogeneity (I^2 >50%). In both cases, the meta-analysis included two or three studies and so there was insufficient data to populate subgroups to complete a subgroup analysis. These outcomes were therefore analysed using a random effects model and were downgraded for inconsistency.

Indirectness

The majority of outcomes in this review were downgraded for indirectness. This was due to one of two reasons:

- Outcome indirectness – the majority of studies had less than 3 months follow up.
- Population indirectness – one study[9] included participants with multiple sclerosis and major depressive disorder. As fatigue can be a symptom of both conditions, this was considered as a source of indirectness.

Meta-analysis

Studies reported continuous outcomes in various ways across and within studies. For example, within a single study the same protocol outcome category could be reported in multiple scales that are not comparable (such as cognitive functions where, the symbol digit modalities test could be reported in the same study as the California verbal learning test-II).

In these cases, all forms of the outcome have been extracted and pooled with other studies reporting outcomes in the same scale.

All studies reported final values. Where possible, parallel and crossover trials have been combined (using generic inverse variance analysis as appropriate).

Studies not using pharmacological interventions specifically for fatigue

Four studies did not specifically use pharmacological interventions to manage fatigue. In these studies, the agents were either used for neuroprotection (Cambron 2016[5], Chataway 2020[7]), depression (Ehde 2008[9]) or for cognitive function (Ford-Johnson 2016[10]). These studies were included in the review as they also investigated the effect on fatigue.

Previously included studies and outcomes

All studies included in the previous version of the guideline were included in this updated version of the review. However, four studies that were published before 2014 but were not included in the previous version of the guideline were included in this review (Ashtari 2009[2], Hamzei-Moghaddam 2011[12], Möller 2011[15] and Stankoff 2005[26]). For Moghaddam 2011[12], Möller 2011[15] and Stankoff 2005[26], this is because they included interventions that were excluded in the previous version of the guideline (combinations of treatments and modafinil respectively) but were relevant to the current review protocol. For Ashtari 2009[2], it is unclear why it was not identified as part of the previous version of this review. A fifth study fulfilled the inclusion criteria but was not included in the previous version of the guideline (Rosenberg 1988[23]). This study was not included as it was a small study (n=10) from before the date limitation which was unlikely to add sufficient data to impact the recommendations from this review. In studies that were previously included in the guideline, some outcomes were not included in analyses. This was either because the outcomes reported in the paper did not fall into categories stated in protocol (such as reporting total adverse events) or because the outcomes were reported in a way where meta-analysis would not be possible and would make interpretation difficult.

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

Of the thirty-two papers excluded from the review after reviewing full texts, this included two Cochrane reviews. These reviews were excluded either because of incorrect population (post-stroke fatigue)[27] or because the systematic review was withdrawn by the Cochrane and PaPaS review group as it did not meet their timelines and expectations[21].

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

1.1.5.1 Amantadine compared to aspirin

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Shaygannejad 2012[25]	Amantadine (n=26) Oral amantadine 100mg twice daily for 4 weeks Aspirin (n=26)	Multiple Sclerosis N = 52 Age (mean [SD]): 35.3 (7.8) years	Patient-reported outcome measures to assess MS fatigue at 3-6 months	This study was included in the previous version of the guideline.

Study	Intervention and comparison	Population	Outcomes	Comments
	Oral aspirin 500mg once daily for 4 weeks Concomitant therapy: All people had received interferon-beta treatment for the past year. Disease modifying treatment status: All participants were receiving disease modifying treatment.	Type of multiple sclerosis: Relapsing-remitting: 44. Secondary progression: 8. EDSS (mean [SD]): 1.6 (1.6) People receiving palliative care: Not stated/unclear.		This study was a crossover trial (two-week washout).

1.1.5.2 Amantadine compared to modafinil

Table 3: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Ledinek 2013[14]	Amantadine (n=15) Amantadine 200mg orally daily for 1 month Modafinil (n=15) Modafinil 200mg orally daily for 1 month Placebo (n=15) A fourth group receiving acetyl-l-carnitine (n=15) was not extracted as it did not fulfil the inclusion criteria in the protocol. Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 60 Age (mean [SD]): 38.0 (6.1) years Type of multiple sclerosis: Not stated/unclear. EDSS: 2.7 (1.1) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Health-related Quality of Life at 3-6 months	This study was included in the previous version of the guideline.

Study	Intervention and comparison	Population	Outcomes	Comments
Nourbakhsh 2021[19] Subsidiary studies: Nourbakhsh 2018[20]	Amantadine (n=141) Oral amantadine (up to 100mg twice daily) Modafinil (n=141) Oral modafinil (up to 100mg twice daily) Placebo (n=141) A fourth group receiving methylphenidate (n=141) was reported. The results for this group was not extracted as they did not fulfil the inclusion criteria in the protocol. Concomitant therapy: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 141 Age (mean [SD]): 46.8 (10.7) years Type of multiple sclerosis: Relapsing-remitting MS: 106 Secondary progressive MS: 19 Primary progressive MS: 15. EDSS (median [IQR]): 3 (2-4.5) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months Cardiac events/arrhythmia at 3-6 months Epworth Sleepiness scale at 3-6 months	Clinicaltrials.gov number: NCT03185065. This study was a crossover trial (two-week washout).

1.1.5.3 Amantadine compared to placebo

Table 4: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Anonymous 1987[1]	Amantadine (n=115) 100mg orally twice a day for 3 weeks (with a 2-week washout period before the study, and a 2-week washout period before crossing over to placebo treatment for 3 weeks). Placebo (n=115)	Multiple Sclerosis N = 115 Age (mean [SE]): 40.8 (1) years Type of multiple sclerosis: Relapsing-remitting: 57 Relapsing/progressing: 33 Chronic progressing: 22 Benign: 3	Adverse events leading to withdrawal at 3-6 months Disruption of sleep at 3-6 months Cardiac events/arrhythmia at 3-6 months Cognitive functions at 3-6 months	Trial by the Canadian MS Research Group. This study was a crossover trial (two-week washout). This study was included in the previous version of the guideline.

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: The only concomitant medications permitted were small doses of muscle relaxants (baclofen, dantrolene) to control spasticity; anticholinergics (oxybutynin) for bladder control; and short-acting benzodiazepines at bedtime. Disease modifying treatment status: Not stated/unclear.	EDSS (mean [SE]): 4.2 (0.2) People receiving palliative care: Not stated/unclear.	Psychological symptoms at 3-6 months	
Ashtari 2009[2]	Amantadine (n=21) Oral amantadine 200mg per day for 2 months Placebo (n=21) Concomitant therapy: No additional information. Disease modifying treatment status: All were receiving treatment with disease modifying agents (either interferon-beta, cytotoxic drugs or a combination of both).	Multiple Sclerosis N = 41 Age (mean [SD]): 25.48 (5.12) years Type of multiple sclerosis: Relapsing-remitting. EDSS (mean [SD]): 2.56 (3.67) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months	
Cohen 1989[8]	Amantadine (n=29) Amantadine 100mg orally twice a day for 4 weeks Placebo (n=29) Concomitant therapy: No additional information	Multiple Sclerosis N = 29 Age (mean [SD]): 44.5 (9.3) years Type of multiple sclerosis: 13 demonstrated a chronic deteriorating or relapsing/deteriorating course of	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months	This study was a crossover trial (two-week washout). This study was included in the previous version of the guideline.

Study	Intervention and comparison	Population	Outcomes	Comments
	Disease modifying treatment status: Not stated/unclear.	illness, while 16 exhibited either a benign or remitting/relapsing course. EDSS: <6 (people with a score >6 were excluded) People receiving palliative care: Not stated/unclear.		
Krupp 1995[13] Subsidiary studies: Geisler 1996[11]	Amantadine (n=31) Amantadine 100mg twice a day for 2 months Placebo (n=35) A third group receiving pemoline (n=27) was not included in this review as they did not fulfil the inclusion criteria in the protocol. Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 93 Age (mean [SD]): 41.1 (6.5) years Type of multiple sclerosis: 90-94% had relapsing-remitting multiple sclerosis EDSS: 2.38 (1.54) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months Sleep disturbance at 3-6 months Cardiac disorder/arrhythmia at 3-6 months Cognitive functions at 3-6 months	The patient-reported outcome measures to assess MS fatigue and cognitive functions outcomes were extracted from Geisler 1996 which only included a subset of the participants included in the original Krupp study (as these values were only reported in a manner that could be meta-analysed in the Geisler study). This study was included in the previous version of the guideline. In the previous version of the guideline these studies were reported separately. Due to the participants in the Geisler study being a subset of those from the Krupp study, they were combined in this analysis for this version.
Ledinek 2013[14]	Amantadine (n=15) Amantadine 200mg orally daily for 1 month Modafinil (n=15) Modafinil 200mg orally daily for 1 month	Multiple Sclerosis N = 60 Age (mean [SD]): 38.0 (6.1) years Type of multiple sclerosis: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Health-related Quality of Life at 3-6 months	This study was included in the previous version of the guideline.

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=15) A fourth group receiving acetyl-l-carnitine (n=15) was not extracted as it did not fulfil the inclusion criteria in the protocol. Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	EDSS: 2.7 (1.1) People receiving palliative care: Not stated/unclear.		
Murray 1985[16]	Amantadine (n=32) Amantadine 100mg orally twice a day for 3 weeks, then placebo orally twice a day for 3 weeks (1 week washout period between doses) Placebo (n=32) Concomitant therapy: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 32 Age (mean [SD]): Not stated/unclear. Type of multiple sclerosis: Not stated/unclear. EDSS: Most of the participants were in the 0-3 range in the EDSS. People receiving palliative care: Not stated/unclear.	Withdrawal due to adverse events at 3-6 months	This study was a crossover trial (1 week washout). This study was included in the previous version of the guideline.
Nourbakhsh 2021[19] (TRIUMPHANT-MS) Subsidiary studies: Nourbakhsh 2018[20]	Amantadine (n=141) Oral amantadine (up to 100mg twice daily) Modafinil (n=141) Oral modafinil (up to 100mg twice daily) Placebo (n=141)	Multiple Sclerosis N = 141 Age (mean [SD]): 46.8 (10.7) years Type of multiple sclerosis: Relapsing-remitting MS: 106 Secondary progressive MS: 19 Primary progressive MS: 15.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months Cardiac events/arrhythmia at 3-6 months Epworth Sleepiness scale at 3-6 months	Clinicaltrials.gov number: NCT03185065. This study was a crossover trial (2-week washout).

Study	Intervention and comparison	Population	Outcomes	Comments
	A fourth group receiving methylphenidate (n=141) was reported. The results for this group was not extracted as they did not fulfil the inclusion criteria in the protocol. Concomitant therapy: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.	EDSS (median [IQR]): 3 (2-4.5) People receiving palliative care: Not stated/unclear.		
Rocca 2021[22]	Amantadine (n=15) Oral amantadine (100mg twice daily for 4 weeks) Placebo (n=15) (One placebo tablet twice daily for 4 weeks) A third group receiving fampridine (n=15) was reported but not extracted as this was not an intervention in the review protocol. Concomitant therapy: Not stated/unclear. Disease modifying treatment status: majority (>80%) were taking these treatments	Multiple Sclerosis N = 30 Age (mean [IQR]): 41.2 (34-46) years in amantadine and 41.9 (33-49) years in placebo Type of multiple sclerosis: Relapsing-remitting MS: all relapsing remitting (inclusion criterion) EDSS (median [IQR]): 2.5 (2 to 2.5) in amantadine group and 2 (1.5 to 2) in placebo group People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months	Trial registration: EudraCT 2010-023678-38.

1.1.5.4 SSRIs compared to placebo

Table 5: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Cambron 2019[4] (FLUOX-PMS trial) Subsidiary studies: Cambron 2016[5]	Fluoxetine (n=74) Fluoxetine 20mg orally for 4 weeks, followed by a daily single intake of 2 tablets of 20mg fluoxetine until week 108. Placebo (n=77) Concomitant therapy: Concomitant medications that could lead to clinically significant interactions with fluoxetine (such as monoamine oxidase inhibitors) were not allowed. The use of interferon beta or glatiramer acetate was allowed, as these drugs are ineffective in slowing down disability accrual in progressive MS. Patients using other immunosuppressive or immunomodulatory drugs could only be included if the drug was stopped at least for 2 months before randomisation. Disease modifying treatment status: People were allowed to use some treatment (see concomitant therapies). However, only around 27% received them.	Multiple Sclerosis N = 151 Age (mean [SD]): 52.6 (7.1) years Type of multiple sclerosis: Primary progressive MS: 77 Secondary progressive MS: 55 EDSS (mean [SD]): 13.3 (8.4) People receiving palliative care: Not stated/unclear	Patient-reported outcome measures to assess MS fatigue at >6 months-1 year Adverse events leading to withdrawal at >6 months-1 year Disruption to sleep at >6 months-1 year Cognitive functions at >6 months-1 year Psychological symptoms at >6 months-1 year	EudraCT Number 2011-003775-11.

Study	Intervention and comparison	Population	Outcomes	Comments
Chataway 2020[7] (MS-SMART trial) Subsidiary studies: Chataway 2015[6]	Fluoxetine (n=111) Fluoxetine 20mg orally once a day for 4 weeks, then twice a day from week 4 to week 96. Placebo (n=112) Two additional groups were reported in the study reporting participants receiving amiloride and riluzole (both n=111). These were excluded from this review as they were not included in the protocol. Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 445 Age (mean [95% CI]): Fluoxetine: 55.5 (50.7 to 60.2) years Placebo: 56.4 (49.2 to 60.4) years Type of multiple sclerosis: Secondary progressive multiple sclerosis. EDSS (mean [95% CI]): Fluoxetine: 6 (5.5 to 6.5) Placebo: 6 (5.5 to 6.5) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at >6 months-1 year Cardiac events/arrhythmia at >6 months-1 year Health-related Quality of Life at >6 months-1 year Cognitive functions at >6 months-1 year	ClinicialTrials.gov registry = NCT01910259.
Edhe 2008[9]	Paroxetine (n=22) Paroxetine 10mg per day, up titrated to 20mg/day after 1 week (2 capsules) and then could be further up titrated a maximum of 40mg/day in subsequent weeks dependent on symptoms or down titrated due to adverse events. Placebo (n=20) Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 42 Age (mean [SD]): 45 (10.1) years Type of multiple sclerosis: Not stated/unclear. EDSS: Mixed. Mild (0-4): 22, Moderate (4.5-6.5): 16, Severe (8-9.5): 4. People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months Health-related Quality of Life at 3-6 months Cognitive functions at 3-6 months Psychological symptoms at 3-6 months	This study was included in the previous version of the guideline.

1.1.5.5 Aspirin compared to placebo

Table 6: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Sadeghi-Naini 2017[24]	Aspirin (n=64) Oral low dose aspirin (80mg) daily for 8 weeks Placebo (n=56) Concomitant therapy: All people were using the different disease modifying therapies including beta-interferons which were prescribed for them. Disease modifying treatment status: All participants were receiving disease modifying therapy.	Multiple Sclerosis N = 120 Age (mean [SD]): 33.2 (9.1) years Type of multiple sclerosis: Relapsing-remitting MS: 80 Secondary progressive MS: 18 Primary progressive MS: 2 EDSS: 1.8 (1.2) People receiving palliative care: Not stated/unclear.	Withdrawal due to adverse events at 3-6 months	

1.1.5.6 Modafinil compared to placebo

Table 7: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Ford-Johnson 2016[10]	Modafinil (n=9) Modafinil 200mg once a day orally for 2 weeks, followed by 1 week washout, then placebo once a day orally for 2 weeks. Placebo (n=9) Concomitant therapy: No additional information.	Multiple Sclerosis N = 18 Age (mean [SD]): 42.44 (8.06) years Type of multiple sclerosis: Relapsing-remitting: 10 Primary progressive: 1 Secondary progressive: 3 Progressive relapsing: 0 Unknown: 2	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months Health-related Quality of Life at 3-6 months Cognitive functions at 3-6 months Psychological symptoms at 3-6 months	Clinicaltrials.gov - NCT00142402.

Study	Intervention and comparison	Population	Outcomes	Comments
	Disease modifying treatment status: Not stated/unclear.	EDSS: 3.9 (2.2) People receiving palliative care: Not stated/unclear.		
Ledinek 2013[14]	Amantadine (n=15) Amantadine 200mg orally daily for 1 month Modafinil (n=15) Modafinil 200mg orally daily for 1 month Placebo (n=15) A fourth group receiving acetyl-l-carnitine (n=15) was not extracted as it did not fulfil the inclusion criteria in the protocol. Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 60 Age (mean [SD]): 38.0 (6.1) years Type of multiple sclerosis: Not stated/unclear. EDSS: 2.7 (1.1) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Health-related Quality of Life at 3-6 months	This study was included in the previous version of the guideline.
Möller 2011[15] (HAGIL study)	Modafinil (n=62) Modafinil oral 200mg/day up titrated over 1 week, then continued for 8 weeks in total. Placebo (n=59) Concomitant therapy: Not stated/unclear. Disease modifying treatment status: Mixed. 50.4% were on immunotherapy.	Multiple Sclerosis N = 121 Age (mean [SD]): 41.1 (10.3) years Type of multiple sclerosis: Relapsing-remitting MS: 63 Secondary-progressive MS: 31 Primary-progressive MS: 26. EDSS: 3.3 (1.4).	Patient-reported outcome measures to assess MS fatigue at 3-6 months Health-related Quality of Lfe at 3-6 months Epworth Sleepiness scale at 3-6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
		People receiving palliative care: Not stated/unclear.		
Nourbakhsh 2021[19] Subsidiary studies: Nourbakhsh 2018[20]	Amantadine (n=141) Oral amantadine (up to 100mg twice daily) Modafinil (n=141) Oral modafinil (up to 100mg twice daily) Placebo (n=141) A fourth group receiving methylphenidate (n=141) was reported. The results for this group was not extracted as they did not fulfil the inclusion criteria in the protocol. Concomitant therapy: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 141 Age (mean [SD]): 46.8 (10.7) years Type of multiple sclerosis: Relapsing-remitting MS: 106 Secondary progressive MS: 19 Primary progressive MS: 15. EDSS (median [IQR]): 3 (2-4.5) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months Withdrawal due to adverse events at 3-6 months Cardiac events/arrhythmia at 3-6 months Epworth Sleepiness scale at 3-6 months	Clinicaltrials.gov number: NCT03185065. This study was a crossover trial (two-week washout).
Stankoff 2005[26]	Modafinil (n=59) Oral modafinil 200mg for 1 week, increased by 100mg every week up to 400mg/day and remaining at that dose between day 31 and day 35 (5 weeks treatment in total). Placebo (n=56) Concomitant therapy: Disease-modifying therapies such as beta interferon,	Multiple Sclerosis N = 115 Age (mean [SD]): 43.9 (8.5) years Type of multiple sclerosis: Relapsing-remitting or progressive MS. EDSS (mean [SD]): 3.5 (1.7) People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS at 3-6 months Withdrawal due to adverse events at 3-6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	glatiramer acetate, azathioprine or methotrexate were allowed, but had to be a stable dose for at least 6 months before treatment. All symptomatic treatment for fatigue had to be withdrawn at least 14 days before randomisation. Disease modifying treatment status: Unclear. People were allowed to continue previous treatment.			

1.1.5.7 Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

Table 8: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Hamzei-Moghaddam 2011[12]	Combination of pharmacological therapies (amantadine and aspirin) (n=21) Amantadine 100mg and aspirin 500mg twice a day for 6 weeks. Amantadine (n=24) Amantadine 100mg and placebo twice a day for 6 weeks. Concomitant therapy: No additional information. Disease modifying treatment status: Not stated/unclear.	Multiple Sclerosis N = 45 Age (mean [SD]): 33.1 (7.5) years Type of multiple sclerosis: Relapsing-remitting: 36. Secondary progressive: 9. EDSS: Mixed EDSS <2: 13. EDSS 2-5: 14. EDSS >5: 18. People receiving palliative care: Not stated/unclear.	Patient-reported outcome measures to assess MS fatigue at 3-6 months	Iranian Randomised Clinical trial number: 201112208430N3.

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Amantadine compared to aspirin

Table 9: Clinical evidence summary: amantadine compared to aspirin

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with aspirin	Risk difference with amantadine
Patient-reported outcome measures to assess MS fatigue (FSS, 1-7, lower values are better, final value, crossover trial) at 3-6 months	52 (1 RCT) follow up: 10 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 3.55	**MD 0.2 higher** (0.63 lower to 1.03 higher)
Explanations a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b. Downgraded by 1 or 2 increments because of outcome indirectness c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

1.1.6.2 Amantadine compared to modafinil

Table 10: Clinical evidence summary: amantadine compared to modafinil

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with modafinil	Risk difference with amantadine
Patient-reported outcome measures to assess MS fatigue (MFIS, 0-	278 (2 RCTs) follow up: mean 5 weeks	⊕◯◯◯ VERY LOW [a,b,c,d]	-	-	**MD 7.51 lower** (27.58 lower to 12.56 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with modafinil	Risk difference with amantadine
84, lower values are better, final value, parallel trial and crossover trial) at 3-6 months					
Withdrawal due to adverse events at 3-6 months (crossover)	252 (1 RCT) follow up: 6 weeks	⨁◯◯◯ VERY LOW [a,c,d]	RR 2.95 (0.31 to 28.01)	8 per 1,000	**16 more per 1,000** (6 fewer to 216 more)
Cardiac events/arrhythmias at 3-6 months (crossover)	252 (1 RCT) follow up: 6 weeks	⨁◯◯◯ VERY LOW [a,c,d]	RR 0.59 (0.14 to 2.42)	40 per 1,000	**16 fewer per 1,000** (34 fewer to 57 more)
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	30 (1 RCT) follow up: 4 weeks	⨁◯◯◯ VERY LOW [a,c,d]	-	The mean health-related Quality of Life was 41.5	**MD 7.1 lower** (12.21 lower to 1.99 lower)
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	30 (1 RCT) follow up: 4 weeks	⨁◯◯◯ VERY LOW [a,c,d]	-	The mean health-related Quality of Life was 42.8	**MD 6 higher** (1.01 higher to 10.99 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with modafinil	Risk difference with amantadine
Epworth Sleepiness scale (0-24, lower values are better, final value, crossover trial) at 3-6 months	248 (1 RCT) follow up: 6 weeks	⨁⨁◯◯ LOW [a,c]	-	The mean Epworth Sleepiness scale was 8.3	MD **1 higher** (0.02 higher to 1.98 higher)
Explanations a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis c. Downgraded by 1 or 2 increments because of outcome indirectness d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

1.1.6.3 Amantadine compared to placebo

Table 11: Clinical evidence summary: amantadine compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
Patient-reported outcome measures to assess MS fatigue (FSS, 1-7, lower values are better, change score and final value, parallel trials) at 3-6 months	74 (2 RCTs) follow up: mean 2 months	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 3.03	**MD 0.56 lower** (0.81 lower to 0.31 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value, parallel trial and crossover trial) at 3-6 months	307 (3 RCTs) follow up: mean 5 weeks	⨁◯◯◯ VERY LOW [a,b,c,d]	-	-	**MD 3.57 lower** (15.06 lower to 7.91 higher)
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - energy level, 1-5, higher values are better, final values, crossover trial) at 3-6 months	44 (1 RCT) follow up: 10 weeks	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 2.76	**MD 0.28 higher** (0.06 higher to 0.5 higher)
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - muscle strength, 1-5, higher values are better, final values, crossover trial) at 3-6 months	44 (1 RCT) follow up: 10 weeks	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 2.75	**MD 0.19 higher** (0.03 lower to 0.41 higher)
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - concentration/memory, 1-5, higher values are	44 (1 RCT) follow up: 10 weeks	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 2.98	**MD 0.42 higher** (0.18 higher to 0.66 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
better, final values, crossover trial) at 3-6 months					
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - motivation level, 1-5, higher values are better, final values, crossover trial) at 3-6 months	44 (1 RCT) follow up: 10 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 2.98	**MD 0.18 higher** (0.06 lower to 0.42 higher)
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - ability to finish task, 1-5, higher values are better, final values, crossover trial) at 3-6 months	44 (1 RCT) follow up: 10 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 3.02	**MD 0.14 higher** (0.1 lower to 0.38 higher)
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - ability to solve problem, 1-5, higher values are better, final values, crossover trial) at 3-6 months	44 (1 RCT) follow up: 10 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 3.13	**MD 0.24 higher** (0.02 lower to 0.5 higher)
Patient-reported outcome measures to assess MS fatigue	44 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome	**MD 0.27 higher** (0.07 higher to 0.47 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
(diary ratings of fatigue - wellbeing, 1-5, higher values are better, final values, crossover trial) at 3-6 months	follow up: 10 weeks			measures to assess MS fatigue was 2.9	
Adverse events leading to withdrawal at 3-6 months (parallel trial and crossover trials)	741 (7 RCTs) follow up: mean 7 weeks	⊕◯◯◯ VERY LOW [a,b,e,f]	RD 0.00 (-0.02 to 0.02)	0 per 1,000	**0 fewer per 1,000** (20 fewer to 20 more) [g]
Disruption of sleep at 3-6 months (parallel trial and crossover trial)	296 (2 RCTs) follow up: mean 6 weeks	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.81 (1.11 to 2.94)	133 per 1,000	**108 more per 1,000** (15 more to 259 more)
Cardiac events/arrhythmias at 3-6 months (parallel trial and crossover trials)	547 (3 RCTs) follow up: mean 6 weeks	⊕◯◯◯ VERY LOW [a,b,e,f]	RD 0.00 (-0.01 to 0.02)	0 per 1,000	**0 fewer per 1,000** (10 fewer to 20 more) [g]
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	30 (1 RCT) follow up: 4 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 41.5	**MD 7.1 lower** (12.21 lower to 1.99 lower)
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value,	30 (1 RCT) follow up: 4 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 40.4	**MD 8.4 higher** (2.9 higher to 13.9 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
parallel trial) at 3-6 months					
Cognitive functions (13-item activities of daily living intellectual function factor, 0-50, lower values are better, final value, crossover trial) at 3-6 months	172 (1 RCT) follow up: 3 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean cognitive functions was 8.25	**MD 0.58 lower** (1.54 lower to 0.38 higher)
Cognitive functions (selective reminding - long-term retrieval, higher values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 45.2	**MD 3 lower** (13.23 lower to 7.23 higher)
Cognitive functions (selective reminding - delayed recall, higher values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 8.9	**MD 0** (2.33 lower to 2.33 higher)
Cognitive functions (selective reminding - sum of recall, higher values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 53.5	**MD 1.2 lower** (7.14 lower to 4.74 higher)
Cognitive functions (Benton Visual Retention, lower values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 2.8	**MD 1.5 higher** (0.03 higher to 2.97 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
Cognitive functions (WAIS-R Digit Span, higher values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 16.5	**MD 0.9 lower** (3.07 lower to 1.27 higher)
Cognitive functions (Trail Making Test - Part A, lower values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 36.2	**MD 5.3 lower** (13.64 lower to 3.04 higher)
Cognitive functions (Trail Making Test - Part B, lower values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 83.1	**MD 14.2 lower** (35.14 lower to 6.74 higher)
Cognitive functions (symbol digit modalities test - written, higher values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 46.6	**MD 2 higher** (8.37 lower to 12.37 higher)
Cognitive functions (symbol digit modalities test - oral, higher values are better, final value) at 3-6 months	32 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 58.3	**MD 0.5 lower** (13.19 lower to 12.19 higher)
Psychological symptoms (Beck Depression Inventory, 0-63, lower values are better, final value,	172 (1 RCT) follow up: 3 weeks	⊕◯◯◯ VERY LOW [a,b]	-	The mean psychological symptoms was 7.59	**MD 0.25 lower** (2.54 lower to 2.04 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with amantadine
crossover trial) at 3-6 months					
Epworth Sleepiness scale (0-24, lower values are better, final value, crossover trial) at 3-6 months	247 (1 RCT) follow up: 6 weeks	⨁⨁◯◯ LOW [a,b]	-	The mean Epworth Sleepiness scale was 9.4	**MD 0.1 lower** (1.08 lower to 0.88 higher)

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of outcome indirectness

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

f. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

g. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1.1.6.4 SSRIs compared to placebo

Table 12: Clinical evidence summary: SSRIs compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SSRIs
Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better,	42 (1 RCT) follow up: 4 months	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean patient-reported outcome measures to assess MS fatigue was 52.1	**MD 12.8 lower** (22.93 lower to 2.67 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SSRIs
final value) at 3-6 months					
Patient-reported outcome measures to assess MS fatigue (Modified fatigue impact scale, Neurological Fatigue Index Summary Score [different scale ranges], lower values are better, final values, parallel trials) at >6 months-1 year	328 (2 RCTs) follow up: mean 54 weeks	⨁⨁⨁⨁ HIGH	-	-	**SMD 0.16 higher** (0.06 lower to 0.37 higher)
Adverse events leading to withdrawal at >6 months-1 year (parallel trial) [d]	137 (1 RCT) follow up: 60 weeks	⨁◯◯◯ VERY LOW [a,c]	RR 0.70 (0.23 to 2.11)	103 per 1,000	**31 fewer per 1,000** (79 fewer to 114 more)
Disruption to sleep at >6 months-1 year (parallel trial) [d]	137 (1 RCT) follow up: 60 weeks	⨁⨁⨁◯ MODERATE [a]	OR 7.28 (0.14 to 367.07)	0 per 1,000	**10 more per 1,000** (20 fewer to 50 more) [e]
Cardiac events/arrhythmias at >6 months-1 year (parallel trial)	223 (1 RCT) follow up: 96 weeks	⨁⨁◯◯ LOW [c,f]	RR 1.51 (0.26 to 8.88)	18 per 1,000	**9 more per 1,000** (13 fewer to 141 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SSRIs
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	42 (1 RCT) follow up: 4 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 35.5	**MD 0.9 higher** (6.87 lower to 8.67 higher)
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	42 (1 RCT) follow up: 4 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 42.5	**MD 5.9 higher** (8.25 lower to 20.05 higher)
Health-related Quality of Life (EQ-5D-5L utility index score, -0.11-1, higher values are better, final value, parallel trial) at >6 months-1 year	194 (1 RCT) follow up: 48 weeks	⊕⊕◯◯ LOW [c]	-	The mean health-related Quality of Life was 0.65	**MD 0.01 higher** (0.04 lower to 0.06 higher)
Health-related Quality of Life (EQ-5D-5L visual analogue scale score, 0-100, higher values are	194 (1 RCT) follow up: 48 weeks	⊕⊕⊕⊕ HIGH	-	The mean health-related Quality of Life was 62.96	**MD 3.18 higher** (2.6 lower to 8.96 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SSRIs
better, final value, parallel trial) at >6 months-1 year					
Cognitive functions (PDQ, 0-100, lower values are better, final value, parallel trial) at 3-6 months	42 (1 RCT) follow up: 4 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 40.4	**MD 11.3 lower** (19.1 lower to 3.5 lower)
Cognitive functions (Symbol digit modalities test, higher values are better, final value, parallel trials) at >6 months-1 year	328 (2 RCTs) follow up: mean 54 weeks	⊕⊕⊕⊕ HIGH	-	The mean cognitive functions was 41.0	**MD 0.77 lower** (3.42 lower to 1.88 higher)
Cognitive functions (California verbal learning test-II, higher values are better, final value, parallel trial) at >6 months-1 year [d]	134 (1 RCT) follow up: 60 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean cognitive functions was 137	**MD 0.5 higher** (8.98 lower to 9.98 higher)
Cognitive functions (Controlled oral word association test - semantic, higher values are better, final value, parallel trial) at >6 months-1 year [d]	134 (1 RCT) follow up: 60 weeks	⊕⊕⊕◯ MODERATE [a]	-	The mean cognitive functions was 20	**MD 0.4 higher** (1.63 lower to 2.43 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SSRIs
Cognitive functions (Controlled oral word association test - phonetic, higher values are better, final value, parallel trial) at >6 months-1 year [d]	134 (1 RCT) follow up: 60 weeks	⨁⨁◯◯ LOW [a,c]	-	The mean cognitive functions was 29.1	**MD 5.5 higher** (1.54 higher to 9.46 higher)
Psychological symptoms (HAM-D, 0-50, lower values are better, final value, parallel trial) at 3-6 months	42 (1 RCT) follow up: 4 months	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean psychological symptoms was 10.9	**MD 4.5 lower** (7.29 lower to 1.71 lower)
Psychological symptoms (Beck depression inventory-II, 0-63, lower values are better, final values, parallel trial) at >6 months-1 year [d]	134 (1 RCT) follow up: 60 weeks	⨁⨁◯◯ LOW [a]	-	The mean psychological symptoms was 11.3	**MD 0.6 higher** (2.1 lower to 3.3 higher)

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of population indirectness

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. This is not downgraded for indirectness as there was a period of 4 weeks where the fluoxetine dose was titrated up that was included in this follow up period. Therefore, the follow up is essentially 1 year.

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

f. Downgraded by 1 or 2 increments due to outcome indirectness

1.1.6.5 Aspirin compared to placebo

Table 13: Clinical evidence summary: aspirin compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with aspirin
Withdrawal due to adverse events at 3-6 months (parallel trial)	120 (1 RCT) follow up: 8 weeks	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.46 (0.36 to 5.83)	54 per 1,000	25 more per 1,000 (34 fewer to 259 more)

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments due to outcome indirectness

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.1.6.6 Modafinil compared to placebo

Table 14: Clinical evidence summary: modafinil compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale Total Score, 0-84, lower values are better,	549 (5 RCTs) follow up: mean 6 weeks	⨁⨁◯◯ LOW [a,b]	-	-	**MD 0.23 lower** (2.68 lower to 2.22 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
final value, parallel trial and crossover trials) at 3-6 months					
Withdrawal due to adverse events (crossover trials) at 3-6 months	285 (2 RCTs) follow up: mean 6 weeks	⊕◯◯◯ VERY LOW [b,c]	RR 1.00 (0.18 to 5.63)	13 per 1,000	**0 fewer per 1,000** (12 fewer to 65 more)
Cardiac events/arrhythmias at 3-6 months (crossover trial)	249 (1 RCT) follow up: 6 weeks	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.65 (0.40 to 6.77)	24 per 1,000	**16 more per 1,000** (15 fewer to 140 more)
Health-related Quality of Life (HAQUAMS, scale range unclear, lower values are better, final value, parallel trial) at 3-6 months	121 (1 RCT) follow up: 8 weeks	⊕⊕◯◯ LOW [b,c]	-	The mean health-related Quality of Life was 11.04	**MD 0.45 higher** (0.59 lower to 1.49 higher)
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	30 (1 RCT) follow up: 4 weeks	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 40.2	**MD 1.3 higher** (3.81 lower to 6.41 higher)
Health-related Quality of Life (SF-36 mental	30 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 40.4	**MD 2.4 higher** (2.59 lower to 7.39 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months	follow up: 4 weeks				
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Bodily pain, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⨁◯◯◯ VERY LOW [b,c]	-	The mean health-related Quality of Life was 7.57	**MD 0** (1.89 lower to 1.89 higher)
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Physical functioning, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⨁⨁⨁◯ MODERATE [b]	-	The mean health-related Quality of Life was 15.54	**MD 6.24 higher** (3.29 higher to 9.19 higher)
Health-related Quality of Life (Multiple Sclerosis Quality of Life	36 (1 RCT) follow up: 2 months	⨁⨁◯◯ LOW [a,b]	-	The mean health-related Quality of Life was 4.57	**MD 2.65 higher** (2.12 higher to 3.18 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
Inventory - role physical, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months					
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - vitality scale, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean health-related Quality of Life was 12	**MD 4.11 higher** (0.2 higher to 8.02 higher)
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - General health, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [b,c]	-	The mean health-related Quality of Life was 17.11	**MD 0.2 higher** (2.63 lower to 3.03 higher)
Health-related Quality of Life (Multiple Sclerosis	36 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	-	The mean health-related Quality of Life was 7.57	**MD 18.54 higher** (16.6 higher to 20.48 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
Quality of Life Inventory - Mental health, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months	follow up: 2 months				
Cognitive functions (Digit Vigilance Test total errors, lower values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive function was 5.55	**MD 1.34 lower** (4.22 lower to 1.54 higher)
Cognitive functions (Weschler Adult Intelligence Scale-III Digit Span Total, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive function was 17.25	**MD 0.63 lower** (3.76 lower to 2.5 higher)
Cognitive functions (Weschler Adult Intelligence Scale-III Letter Number Sequencing, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [b,c]	-	The mean cognitive function was 11	**MD 0.06 lower** (2.35 lower to 2.23 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
Cognitive functions (symbol digit modalities test, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 51.13	**MD 0.32 lower** (9.5 lower to 8.86 higher)
Cognitive functions (California Verbal Learning Test - Second Edition, higher values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean cognitive functions was 52.75	**MD 2.56 lower** (10.9 lower to 5.78 higher)
Psychological symptoms (The State Trait Anxiety Inventory, 0-60, lower values are better, final value, crossover trial) at 3-6 months	36 (1 RCT) follow up: 2 months	⊕⊕◯◯ LOW [b,c]	-	The mean psychological symptoms was 25.56	**MD 1.5 lower** (6.82 lower to 3.82 higher)
Psychological symptoms (Chicago Multiscale Depression Inventory Total Score, scale range unclear, higher values are better, final value,	36 (1 RCT) follow up: 2 months	⊕◯◯◯ VERY LOW [b,c]	-	The mean psychological symptoms was 67.32	**MD 0.37 higher** (12.01 lower to 12.75 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with modafinil
crossover trial) at 3-6 months					
Epworth Sleepiness scale (0-24, lower values are better, final values, parallel trial and crossover trial) at 3-6 months	368 (2 RCTs) follow up: 7 weeks	⨁⨁⨁◯ MODERATE [b]	-	-	**MD 0.78 lower** (1.62 lower to 0.07 higher)
Explanations [a]. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias [b]. Downgraded by 1 or 2 increments due to outcome indirectness [c]. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

1.1.6.7 Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

Table 15: Clinical evidence summary: combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amantadine	Risk difference with combination of pharmacological therapies (amantadine and aspirin)
Patient-reported outcome measures to assess MS fatigue	45 (1 RCT) follow up: 6 weeks	⨁⨁⨁◯ MODERATE [a]	-	The mean patient-reported outcome measures to assess MS fatigue was 3.96	**MD 0.6 lower** (0.89 lower to 0.31 lower)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amantadine	Risk difference with combination of pharmacological therapies (amantadine and aspirin)
(FSS score, 1-7, lower values are better, final values, parallel trial) at 3-6 months					
Explanations a. Downgraded by 1 or 2 increments due to outcome indirectness					

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

Table 16: Unit cost of drugs for the management of fatigue

Drug	Daily dose	Cost per day (f)	Cost per month	Cost per year
Amantadine (capsule)	200-400mg (a)	£0.96-£0.1.92	£29.19-£53.38	£350.27-£700.54
Fluoxetine (tablet)	20-40mg (b)	£0.04-£0.06	£1.14-£1.83	£13.63-£21.90
Paroxetine (capsule)	10-40mg (c)	£0.15-£0.11	£4.64-£3.39	£55.66-£40.64
Aspirin (tablet)	75mg (d)	£0.05	£1.50	£17.99
Modafinil (tablet)	200-400mg (e)	£0.22-£0.43	£6.54-£13.08	£78.48-£156.95

(a) BNF[3], accessed February 2021. 100 mg daily for 1 week, dose to be taken in the morning, then increased to 100 mg twice daily: maximum 400 mg per day.

(b) 20mg orally once a day for 4 weeks, then up titrated to 40mg a day[3, 6]

(c) 10mg daily, up titrated to 20mg/day after 1 week with a maximum dose of 40mg/day in subsequent weeks dependent on symptoms or down-titrated due to adverse events[9]. Note 10mg capsule is more expensive than 20mg tablet.

(d) BNF[3]. Accessed 25/02/2021: 75 mg once daily. Oral low dose aspirin (80mg tablets) daily for 8 weeks[22].

(e) 200mg daily for 1 month, adjusted according to response to 200–400 mg/day[10, 14, 15, 19, 26].

(f) BNF[3]. Accessed 25/02/2021

For modafinil, the BNF states that an electrocardiogram (ECG) is required before initiation. The unit cost of an ECG is £61.80 (NHS reference cost 2019/2020,[18] currency code: EY51Z).

1.1.11 Evidence statements

Effectiveness

See summary of evidence in Tables 14-20.

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 agreed that all outcomes included in the protocol were of critical importance for decision-making. The outcomes included patient-reported measures to assess MS fatigue, Visual Analogue Scale (VAS), adverse effects of treatment, Health-related Quality of Life (HRQoL), impact on patients and carers, cognitive functions, and psychological symptoms assessed by validated and disease-specific scales or questionnaires.

No evidence from randomised controlled trials was identified for VAS or impact on patients/carers.

1.1.12.2 The quality of the evidence

Seventeen randomised controlled trials including all 8 studies from the previous guideline were included in the review. Twelve of these were parallel trials and 5 were crossover trials. Evidence was available for the following comparisons:

- Amantadine compared to aspirin
- Amantadine compared to modafinil
- Amantadine compared to placebo
- SSRIs compared to placebo (analysed as a class, the formulations included are):
  - Fluoxetine compared to placebo
  - Paroxetine compares to placebo
- Aspirin compared to placebo
- Modafinil compared to placebo
- Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

There was no evidence available comparing any intervention with usual care or clinical effectiveness beyond 6 months. There was limited evidence comparing active treatments to each other and comparing combinations of treatments to other treatments and placebo. There was also very limited evidence on adverse events.

In general, the quality of the evidence as assessed by GRADE was very low. Downgrading was most often due to indirectness for follow up as the majority of studies had a follow up time of less than 3 months and did not fulfil a period of 3-6 months as stated in the protocol. In addition, risk of bias due to selection or attrition bias was another reason for downgrading the evidence. In some scenarios, baseline values were different which could have influenced the effect on the meta-analysis. This information was presented to the committee to inform their confidence in the relative treatment effect. Imprecision in the outcomes was common. There was inconsistency in the evidence for Modified Fatigue Impact Scale in studies comparing amantadine to modafinil and for studies comparing amantadine to placebo with statistical heterogeneity being present. In these scenarios, only two or three studies were included in the meta-analysis and therefore there was an insufficient number of studies to produce substantial subgroups for a subgroup analysis. Therefore, the outcomes were analysed using random effects and downgraded for inconsistency.

1.1.12.2.1 Amantadine compared to aspirin

One outcome was reported (patient-reported outcome measures to assess MS fatigue at 3-6 months) including one small study (N=52). This outcome was rated as very low quality due to risk of bias, outcome indirectness and imprecision.

1.1.12.2.2 Amantadine compared to modafinil

Six outcomes were reported, including evidence from two studies. The outcomes were all of very low quality (apart from Epworth Sleepiness Scale at 3-6 months which was of low quality) and were commonly downgraded for risk of bias, outcome indirectness and imprecision. The patient-reported outcome measures to assess MS fatigue outcome was downgraded for inconsistency due to heterogeneity in the outcome.

1.1.12.2.3 Amantadine compared to placebo

Twenty-six outcomes were reported, including evidence from eight studies. The outcomes were all of very low quality (apart from Epworth Sleepiness Scale at 3-6 months which was of low quality) and were commonly downgraded for risk of bias, outcome indirectness and imprecision. The patient-reported outcome measures to assess MS fatigue outcome was downgraded for inconsistency due to heterogeneity in the outcome. The adverse events leading to withdrawal and cardiac events/arrhythmias outcomes were also downgraded for inconsistency due to zero events in some, but not all, studies included in the meta-analysis.

1.1.12.2.4 SSRIs compared to placebo

Sixteen outcomes were reported, including evidence from 3 studies. The outcomes ranged from high to very low quality, with the majority being of moderate-low quality. Outcomes were commonly downgraded for risk of bias, population or outcome indirectness (in this case, population indirectness is due to the inclusion of participants who have major depressive disorder as well as multiple sclerosis, and outcome indirectness being due to the outcome being at a later time period than 1 year).

1.1.12.2.5 Aspirin compared to placebo

One outcome was reported (withdrawal due to adverse events at 3-6 months) including one study (N=120). This outcome was rated as very low quality due to risk of bias, outcome indirectness and imprecision.

1.1.12.2.6 Modafinil compared to placebo

Twenty outcomes were reported, including evidence from five studies. The outcomes ranged from moderate to very low quality, with the majority of outcomes being of very low quality. Outcomes were commonly downgraded for risk of bias, outcome indirectness and imprecision.

1.1.12.2.7 Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

One outcome was reported (patient-reported outcome measures to assess MS fatigue at 3-6 months) including one small study (N=45). This was of moderate quality, being downgraded for outcome indirectness.

1.1.12.3 Benefits and harms

1.1.12.3.1 Amantadine

The effects of amantadine were investigated in ten studies and was compared to: aspirin, modafinil, combination of pharmacological therapies (amantadine and aspirin) and placebo. When compared to placebo at 3-6 months the evidence was mixed. Five outcomes (including evidence from three studies) reported a clinically important benefit for patient reported outcome measures to assess MS fatigue. There was a further patient-reported outcome measure assessing MS fatigue where the overall result of three pooled studies was ‘no clinically important difference’ between the two groups, but there was heterogeneity with one study suggesting better outcome with amantadine, one suggesting very little difference and

the other suggesting worse outcome in the amantadine group. A clinically important benefit was also seen for the mental component of the SF-36 (health-related quality of life). However, the evidence for both outcomes was unclear as for patient reported outcome measures to assess MS fatigue three outcomes (including evidence from one study) showed no clinically important difference, and the physical component of SF-36 showed a clinically important harm. No clinically important difference was seen in withdrawal due to adverse events, cardiac events/arrhythmias, psychological symptoms and Epworth sleepiness scale. The evidence was unclear for cognitive functions, where one outcome showed a clinically important harm but 9 showed no clinically important difference. Disruption of sleep was observed to cause a clinically important harm (in two studies); disruption of sleep was noted to be due to insomnia in studies. Evidence was not available at the more than 6 months to 1 year time-point.

When compared to other interventions at 3-6 months, there was limited evidence. Amantadine appeared to be superior to modafinil in patient reported outcome measures to assess MS fatigue in one outcome populated by two studies. Otherwise, the same effects seen when compared to placebo were apparent for withdrawal due to adverse events, cardiac events/arrhythmias, health-related quality of life and the Epworth sleepiness scale. When compared to aspirin there was no clinically important difference between the two in patient reported outcome measures to assess MS fatigue. When compared to a combination of amantadine and aspirin, amantadine alone was inferior to the combination in patient reported outcome measures to assess MS fatigue, based on evidence from one study including 45 participants. Evidence was not available at the more than 6 months to 1 year time-point.

The committee discussed the heterogeneity in the patient-reported outcome measures to assess MS fatigue outcomes when compared to placebo. They noted that the Nourbakhsh 2021 study, a more recent study with a larger number of participants, showed no clinically important difference when compared to the other studies that showed clinically important benefits. They noted the limitations in this interpretation (as the Nourbakhsh study was a crossover trial with four study arms with a short treatment period for each intervention of 6 weeks). An additional, parallel trial (Rocca 2021) that reported the outcome at only 4 weeks suggested worse outcome with amantadine compared to the placebo group difference. This study consisted of only 15 participants in each arm. They concluded that while overall the evidence showed a clinically important benefit of amantadine, the quality of the evidence was very low and so they could not be confident in the result.

The committee discussed the clinically important harm in disruption of sleep with amantadine compared to placebo. Sleep disturbance is a common side effect of amantadine. In the included studies, amantadine was taken twice daily. Clinical experience stated that amantadine can cause sleep disturbance if taken before sleeping, as by treating fatigue it will cause disruption to sleep. The studies did not state when amantadine was taken. The committee noted that amantadine should be taken earlier in the day to minimise the possibility of sleep disturbance.

The committee noted their experiences with amantadine for fatigue. Currently amantadine is used as an initial treatment for fatigue. Lay member and clinician experience stated that amantadine can be an effective treatment for some people, but not for everyone. Currently it is unknown as to whether there are specific groups of people where this treatment would be more effective.

Based on this evidence the committee concluded that there appear to be benefits from amantadine with harms that likely could be minimised through giving people clear instructions on when to take amantadine. However, they noted the very low quality of the evidence.

1.1.12.3.2 SSRIs

The effects of SSRIs were investigated in three studies and was compared to placebo only. At 3-6 months the evidence was limited (being based on one study with 42 participants). This showed clinically important benefits in patient reported outcome measures to assess MS fatigue, the mental component of SF-36 (health-related quality of life), cognitive functions and psychological symptoms. There was no clinically important difference in the physical component of SF-36. Evidence from 2 studies was available at the more than 6 months to 1 year time-point. However, this evidence showed no clinically important differences in patient reported outcome measures to assess MS fatigue (based on high quality evidence), withdrawal due to adverse events, disruption of sleep, cardiac events/arrhythmias, health-related quality of life, cognitive functions and psychological symptoms.

The committee noted that benefits were seen for SSRIs at 3-6 months. However, the quality of the evidence was very low and based on one small study, which meant they were less confident in the result. Contrarily, at the more than 6 months to 1 year time-point there were no clinically important differences seen based on 2 larger studies with evidence that varied between high and very low quality. The committee agreed that there are potential benefits from using SSRIs for fatigue with no harms being found in this review.

1.1.12.3.3 Aspirin

The evidence on the effects of aspirin was very limited. Aspirin was compared to amantadine and placebo. When compared to placebo the only outcome reported that could be extracted as per the protocol was withdrawal due to adverse events, which showed no clinically important difference based on one study. When compared to amantadine, aspirin showed no clinically important difference in patient-reported outcome measures to assess MS fatigue. These outcomes were all at 3-6 months, with no evidence being available at the more than 6 months to 1 year time-point.

The committee noted there was an absence of evidence for this intervention. Experiences of the committee members noted that aspirin may be given by some people to treat inflammatory pain before exercise rather than to treat fatigue itself. In doing this, and reducing pain, it may help people to exercise more before feeling fatigued. As there was no evidence to show clinical benefit, the committee decided to not make a recommendation on aspirin. Instead, they made a research recommendation in order to investigate this further in the future.

1.1.12.3.4 Modafinil

The effects of modafinil were investigated in five studies and was compared to amantadine and placebo. When compared to placebo at 3-6 months, there was an unclear effect on health-related quality of life, with a clinically important benefit in four outcomes (based on one small study with 36 participants) while there was no clinically important difference in five outcomes (based on three studies). For all other outcomes there was no clinically important difference, including: patient reported outcome measures to assess MS fatigue, withdrawal due to adverse events, disruption of sleep, cardiac events/arrhythmias, cognitive function, psychological symptoms and Epworth sleepiness scale. There was no evidence available at the more than 6 months to 1 year time-point.

When compared to amantadine at 3-6 months, there was limited evidence. Modafinil appeared to be inferior to amantadine in patient reported outcome measures to assess MS fatigue in one outcome populated by two studies. There was an unclear effect on health-related quality of life (based on one small study with 30 participants) where modafinil appeared to be superior in the physical component of SF-36 (health-related quality of life) and inferior in the mental component of SF-36. Otherwise, the same effects seen when compared to placebo were apparent for withdrawal due to adverse events, cardiac

events/arrhythmias and the Epworth sleepiness scale. There was no evidence available at the more than 6 months to 1 year time-point.

The committee acknowledged that there was limited evidence showing a benefit for health-related quality of life only. However, the quality for all outcomes was between moderate and very low, therefore they were ultimately not confident in the results. The committee noted that although modafinil is commonly prescribed in secondary care, the person should be offered modafinil as a first line option. In the committee's experience, modafinil could be particularly effective for people with excessive sleepiness. This subgroup was not investigated in this review.

Based on the absence of harms and potential benefits, modafinil was included in the list of drugs to be considered for people with MS wishing to try a medicine for fatigue. The committee noted that the evidence was of low quality and that, based on clinical experience and consensus within the committee, there may be specific groups of people that would benefit more from modafinil (for example, people with fatigue and excessive sleepiness). Based on this, they made a research recommendation to gain more information about groups where this treatment could be more effective.

Amantadine, SSRIs and modafinil were all recommended as first line options for the treatment of fatigue. Due to the lack of evidence the committee were unable to suggest a preference for what medication should be tried first and emphasised that individual patient factors need to be taken into consideration when discussing options. Response should be monitored and reviewed so that people do not remain on ineffective treatment.

1.1.12.3.5 Combination of pharmacological therapies (amantadine and aspirin)

There was very limited evidence on the efficacy of combination of pharmacological therapies. One study reported comparing amantadine and aspirin to amantadine alone at 3-6 months. In this there was a clinically important benefit of the combination of pharmacological therapies in patient reported outcome measures to assess MS fatigue (based on one small study including 45 participants). There was no evidence available at the more than 6 months to 1 year time-point.

The committee noted the limited evidence for this comparison and for aspirin alone compared to placebo. Based on this they decided to not make a recommendation discussing combinations of pharmacological therapies. Instead, they made a research recommendation in order to investigate this further in the future.

1.1.12.4 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review; therefore, unit costs were presented to aid committee consideration of cost-effectiveness. The annual unit cost of amantadine ranged between approximately £350 and £701, which was significantly more expensive than the other drugs in the clinical studies. The estimated cost of modafinil was between £78 and £157 per year, in addition there is a one of cost of an ECG prior to drug initiation (£62). Aspirin was less costly at £18 per year while the SSRIs fluoxetine and paroxetine were costed at £14-£22 and £56-£41 per year, respectively.

Amantadine
The clinical evidence summarised in the section above reported a clinically important benefit for patient reported outcome measures to assess MS fatigue for amantadine vs placebo. A clinically important benefit was also seen for the mental component of the SF-36 (health-related quality of life). A clinically important harm was reported in disruption of sleep with amantadine compared to placebo. The committee noted that this likely could be minimised through giving people clear instructions on when to take amantadine. There was limited evidence comparing amantadine to other comparators. The previous MS guideline made an 'offer' recommendation for the use of amantadine to treat fatigue in people with MS,

however, it was noted that the cost of amantadine had increased since the development of the last guideline. Experiences of committee members noted that amantadine is usually the conventional treatment for MS-related fatigue and can be an effective treatment for some people, but not for everyone. At the current cost, prescribing amantadine is likely to have a substantial resource impact, as annual costs start at £350, and any treatment costing over £100 affecting 10% of the MS population would be considered a substantial resource impact. Given the lack of published health economic evidence, the increased cost and the very low quality of clinical evidence, a 'consider' recommendation was made for amantadine.

Modafinil
The committee acknowledged that there was limited or unclear evidence showing the benefit of modafinil in terms of health-related quality of life when compared to placebo or amantadine. Some committee members suggested there could be potential improvements to quality of life in terms of employment, as this would improve productivity for people with MS, however, there was no clinical evidence for this and health economic evidence for NICE guidelines does not consider the impact of employment in terms of GDP or productivity of the workforce. The committee acknowledged that there would be a resource impact for recommending modafinil, however, they highlighted that a lower dose (100mg) than what was shown in the studies is commonly prescribed. If 10% of people with MS were treated with the lower dose (~£40 per year) then this would be below the threshold of what is considered a substantial resource impact. Given the limited clinical evidence and lack of cost-effective evidence the committee agreed on a 'consider' recommendation for modafinil.

SSRIs
Clinically important benefits were reported for patient reported outcome measures to assess MS fatigue, the mental component of SF-36 (health-related quality of life), cognitive functions and psychological symptoms. Both SSRIs were also less costly than amantadine. No clinically important harms were found in the clinical review, however, the quality of evidence for benefits seen for SSRIs at 3-6 months was very low and based on one study. Given the potential benefits from SSRIs for fatigue and lack of serious adverse events based on the clinical review, committee agreed on a 'consider' recommendation for SSRIs.

Aspirin
Experiences of committee members noted that aspirin would not be given to treat fatigue specifically but rather to alleviate inflammatory pain before exercising. Alongside this, there was no evidence of clinical benefit of aspirin for treating fatigue and as such the committee agreed not to make a recommendation for the use of aspirin to manage MS-related fatigue.

In conclusion, based on the limited clinical and economic evidence, the committee agreed to make a consider recommendation for amantadine, modafinil and SSRIs. In terms of current practice, amantadine is currently the first-line pharmacological treatment and modafinil is mostly provided in secondary care settings. Given that all three drugs are considered equally, there may be a decrease in use of amantadine and increase in use of modafinil and SSRIs. Given that the unit cost of amantadine is greater than that of modafinil and SSRIs the resource impact of this recommendation is unlikely to be significant.

1.1.12.5 Other factors the committee took into account

The committee noted that currently modafinil is mostly prescribed by secondary care physicians, while amantadine is prescribed by a range of professionals across sectors. Through this recommendation, they believe that practice may change and so modafinil may be prescribed more by different professionals and in primary care.

The committee noted the safety concerns for modafinil, including that it should not be used during pregnancy and that precautions should be taken if prescribing it for women able to

have children, in line with the 2020 MHRA safety advice on modafinil. The committee noted additional advice on monitoring, stopping treatment and cautions for use in the 2014 MHRA safety advice on modafinil and in the summary of product characteristics for modafinil and amantadine.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.12 to 1.5.16 and the research recommendation on pharmacological management of fatigue.

1.1.14 References

1. Anonymous. A randomized controlled trial of amantadine in fatigue associated with multiple sclerosis. Canadian Journal of Neurological Sciences. 1987; 14(3):273-278

2. Ashtari F, Fatehi F, Shaygannejad V, Chitsaz A. Does amantadine have favourable effects on fatigue in Persian patients suffering from multiple sclerosis? Polish Journal of Neurology and Neurosurgery. 2009; 43(5):428-432

3. 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.

4. Cambron M, Mostert J, D'Hooghe M, Nagels G, Willekens B, Debruyne J et al. Fluoxetine in progressive multiple sclerosis: The FLUOX-PMS trial. Multiple Sclerosis. 2019; 25(13):1728-1735

5. Cambron M, Mostert J, Parra J, D'Hooghe M, Nagels G, Willekens B et al. Fluoxetine in progressive multiple sclerosis (FLUOX-PMS). Multiple Sclerosis. 2016; 22(Suppl 3):832-833

6. Chataway J, Chandran S, Miller D, Giovannoni G, Wheeler-Kingshott C, Pavitt S et al. The MS-smart trial in secondary progressive multiple sclerosis: A multi-arm, multi-centre trial of neuroprotection. Journal of Neurology, Neurosurgery and Psychiatry. 2015; 86:e4

7. Chataway J, De Angelis F, Connick P, Parker RA, Plantone D, Doshi A et al. Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. The Lancet Neurology. 2020; 19(3):214-225

8. Cohen RA, Fisher M. Amantadine treatment of fatigue associated with multiple sclerosis. Archives of Neurology. 1989; 46(6):676-680

9. Ehde DM, Kraft GH, Chwastiak L, Sullivan MD, Gibbons LE, Bombardier CH et al. Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis. General Hospital Psychiatry. 2008; 30(1):40-48

10. Ford-Johnson L, DeLuca J, Zhang J, Elovic E, Lengenfelder J, Chiaravalloti ND. Cognitive effects of modafinil in patients with multiple sclerosis: A clinical trial. Rehabilitation Psychology. 2016; 61(1):82-91

11. Geisler MW, Sliwinski M, Coyle PK, Masur DM, Doscher C, Krupp LB. The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis. Archives of Neurology. 1996; 53(2):185-188

12. Hamzei-Moghaddam A SBIFAM. Therapeutic effect of co-administration of amantadine and aspirin on fatigue in patients with multiple sclerosis: A randomized placebo-controlled double-blind study. Iranian Journal of Pharmacology and Therapeutics. 2011; 10(2):71-75

13. Krupp LB, Coyle PK, Doscher C, Miller A, Cross AH, Jandorf L et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. Neurology. 1995; 45(11):1956-1961

14. Ledinek AH, Sajko MC, Rot U. Evaluating the effects of amantadin, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis - result of a pilot randomized, blind study. Clinical Neurology and Neurosurgery. 2013; 115(Supp 1):S86-89

15. Möller F, Poettgen J, Broemel F, Neuhaus A, Daumer M, Heesen C. HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis. Multiple Sclerosis. 2011; 17(8):1002-1009

16. Murray TJ. Amantadine therapy for fatigue in multiple sclerosis. Canadian Journal of Neurological Sciences. 1985; 12(3):251-254

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

18. NHS England and NHS Improvement. 2019/20 National Cost Collection Data Publication. 2021. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ Last accessed: 04 October 2021.

19. Nourbakhsh B, Revirajan N, Morris B, Cordano C, Creasman J, Manguinao M et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. The Lancet Neurology. 2021; 20(1):38-48

20. Nourbakhsh B, Revirajan N, Waubant E. Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS): Study design for a pragmatic, randomized, double-blind, crossover clinical trial. Contemporary Clinical Trials. 2018; 64:67-76

21. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD008427. DOI: 10.1002/14651858.cd008427.pub3.

22. Rocca MA, Valsasina P, Colombo B, Martinelli V, Filippi M. Cortico-subcortical functional connectivity modifications in fatigued multiple sclerosis patients treated with fampridine and amantadine. European Journal of Neurology. 2021; 28(7):2249-2258

23. Rosenberg GA, Appenzeller O. Amantadine, fatigue, and multiple sclerosis. Archives of Neurology. 1988; 45(10):1104-1106

24. Sadeghi-Naini M, Ghazi-zadeh Esslami G, Fayyazi S, Nabavi SM, Morsali D, Ghaffarpour M. Low dose aspirin for MS-related fatigue: Results of a pilot, double-blind, randomized trial. Neurology Psychiatry and Brain Research. 2017; 25:24-30

25. Shaygannejad V, Janghorbani M, Ashtari F, Zakeri H. Comparison of the effect of aspirin and amantadine for the treatment of fatigue in multiple sclerosis: a randomized, blinded, crossover study. Neurological Research. 2012; 34(9):854-858

26. Stankoff B, Waubant E, Confavreux C, Edan G, Debouverie M, Rumbach L et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology. 2005; 64(7):1139-1143

27. Wu S, Kutlubaev MA, Chun HYY, Cowey E, Pollock A, Macleod MR et al. Interventions for post-stroke fatigue. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD007030. DOI: 10.1002/14651858.cd007030.pub3.

Appendices

Appendix A – Review protocols

Review protocol for pharmacological management of fatigue

ID	Field	Content
0.	PROSPERO registration number	CRD42021229697
1.	Review title	Pharmacological management of fatigue
2.	Review question	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of pharmacological interventions for fatigue?
3.	Objective	To determine the most effective and safe pharmacological treatment for fatigue in people with MS
4.	Searches	Key papers Aspirin before exercise Leavitt VM, Blanchard AR, Guo CY, et al. Aspirin is an effective pretreatment for exercise in multiple sclerosis: a double-blind randomized controlled pilot trial. Mult Scler. 2017 Oct 27 [Epub ahead of print]. Wingerchuk DM, Benarroch EE, O'Brien PC, et al. A randomized controlled crossover trial of aspirin for fatigue in multiple sclerosis. Neurology. 2005;64(7):1267-1269. The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		• Epistemonikos Searches will be restricted by: • Date limitations – 2014 onwards (date of publication of CG 186) • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Multiple Sclerosis
6.	Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care, who are experiencing fatigue. Exclusion: Children and young people (≤18 years).
7.	Intervention	• Amantadine • SSRIs • Aspirin specifically before exercise • Modafinil • Combinations of the above
8.	Comparator	Interventions will be compared to each other (both within and between classes), placebo/sham, or usual care.

9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion if they have an appropriate washout period of at least 1 week. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non randomised trials: we consider RCT data to be the best evidence for reviews of interventions. In addition, the surveillance review and GC have highlighted the existence of relevant RCTs in this area. Therefore, if no RCT data is available observational data will not be considered due to the risk of confounding variables influencing the study results, reducing our confidence in the overall results of the review. Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	This review will inform the update of the following recommendations in CG 186. 1.5.2. Assess and offer treatment to people with MS who have fatigue for anxiety, depression, difficulty in sleeping, and any potential medical problems such as anaemia or thyroid disease. 1.5.3 Explain that MS-related fatigue may be precipitated by heat, overexertion and stress or may be related to the time of day. 1.5.4 Offer amantadine to treat fatigue in people with MS.

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical.
		
		• Patient-reported outcome measures to assess MS fatigue, including MFIS Fatigue Severity Scale (FSS), National Fatigue Index (NFI), MS-specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS),
		• Visual Analogue Scale (VAS)
		• Adverse effects of treatment.
		  ○ Adverse events leading to withdrawal
		  ○ Disruption of sleep
		  ○ cardiac events/arrhythmias
		
		• Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale.
		• Impact on patients/carers.
		• Cognitive functions, such as memory and concentration
		• Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments.
		• Epworth sleepiness scale
		
		Follow up:
		• 3-6 months (minimum of 3 months but can include 1-3 months and downgrade)
		• >6 months – 1 year (data from >1 year follow up may be included but will be downgraded)

13.	Secondary outcomes (important outcomes)	n/a (see above)

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

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

<table>
<tr><td></td><td></td><td colspan="3">• According to disability (EDSS <6 and EDSS ≥6)
• Disease modifying treatment status (currently using and not currently using)
• Drug doses (standard doses vs non-standard doses which will be discussed and agreed with the GC prior to presenting the evidence to them)
• Routes of administration (if applicable)
• People receiving palliative care</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">October 2020</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">July 2022</td></tr>
<tr><td rowspan="3">23.</td><td rowspan="3">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>x</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
</table>

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail MultipleSclerosisUpdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Dr Sharon Swain [Guideline lead] Dr Saoussen Ftouh [Senior systematic reviewer] Nicole Downes [Systematic reviewer] Sophia Kemmis Betty [Senior health economist] Lina Gulhane [Information specialist] Emma Clegg [Information specialist] Kate Ashmore [Project Manager]		

26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Multiple sclerosis, fatigue, pharmacological management, amantadine, SSRIs, aspirin specifically before exercise, modafinil
33.	Details of existing review of same topic by same authors	

34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[17] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

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

Appendix B : Literature search strategies

This literature search strategy was used for the following review:

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

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[17]

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

B.1 Clinical search literature search strategy

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

Table 17: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp 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.	aspirin/
42.	(Aspirin or Acetylsalicylic acid or ASA or Acetysal or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetyloxy benzoic Acid).ti,ab.
43.	exp Amantadine/
44.	(Amantadin* or Lysovir or Symmetrel or Aman or merz or ratiopharm or neuraxpharm or amantahciazu or amanta or mantadix or cerebramed or amantadinratiopharm or tregor or midantan or pmsamantadine or wiregyt or "1 aminoadamantane" or ratiopharm or azupharma or amantasulfateazu or adamantylamine or endantadine or symadine or genamantadine or amixx or adekin or viregyt or gen-amantadine or infex).ti,ab.
45.	exp Serotonin Uptake Inhibitors/ or Citalopram/ or Paroxetine/ or fluoxetine/ or Modafinil/
46.	(SSRI* or Citalopram or Cytalopram or Cipramil or Cipralex or Lexapro or escitalopram or Fluoxetine or Prozac or oxactin or prozit or Fluvoxamine or Faverin or sarafem or Paroxetine or Seroxat or Sertraline or Lustral or paxil or aropax or modafanil or

	Armodafanil or Buproprion or Methylphenadite or Dextroamphetamine or Zolpidem or Venlafaxine).ti,ab.
47.	((serotonin or inhibitor) adj2 (uptake or reuptake)).ti,ab.
48.	exp Vitamin B 12/ or Hydroxocobalamin/
49.	(((B-12 or B12) adj1 vitamin) or cyanocobalamin or cobamide* or cobalamin* or eritron or cytamen or hydroxycobalamin).ti,ab.
50.	or/41-49
51.	40 and 50

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.	*acetylsalicylic acid/
40.	(Aspirin or Acetylsalicylic acid or ASA or Acetysal or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetyloxy benzoic Acid).ti,ab.
41.	amantadine/
42.	(Amantadin* or Lysovir or Symmetrel or Aman or merz or ratiopharm or neuraxpharm or amantahciazu or amanta or mantadix or cerebramed or amantadinratiopharm or tregor or midantan or pmsamantadine or wiregyt or "1 aminoadamantane" or ratiopharm or azupharma or amantasulfateazu or adamantylamine or endantadine or symadine or genamantadine or amixx or adekin or viregyt or gen-amantadine or infex).ti,ab.
43.	serotonin uptake inhibitor/ or Citalopram/ or Paroxetine/ or fluoxetine/ or Modafinil/
44.	(SSRI* or Citalopram or Cytalopram or Cipramil or Cipralex or Lexapro or escitalopram or Fluoxetine or Prozac or oxactin or prozit or Fluvoxamine or Faverin or sarafem or Paroxetine or Seroxat or Sertraline or Lustral or paxil or aropax or modafanil or Armodafanil or Buproprion or Methylphenadite or Dextroamphetamine or Zolpidem or Venlafaxine).ti,ab.
45.	((serotonin or inhibitor) adj2 (uptake or reuptake)).ti,ab.
46.	cyanocobalamin/ or hydroxocobalamin/
47.	(((B-12 or B12) adj1 vitamin) or cyanocobalamin or cobamide* or cobalamin* or eritron or cytamen or hydroxycobalamin).ti,ab.
48.	or/39-47
49.	38 and 48

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):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: [Demyelinating Diseases] this term only
#9.	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only
#10.	(Demyelinat* NEAR/2 (syndrome* or disease* or autoimmun*)):ti,ab
#11.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI):ti,ab
#12.	MeSH descriptor: [Venous Insufficiency] this term only and with qualifier(s): [diagnostic imaging - DG, cerebrospinal fluid - CF, complications - CO, diagnosis - DI, etiology - ET]
#13.	(Devic* NEXT (disease or syndrome)):ti,ab
#14.	((clinical* NEXT isolat*) NEXT syndrome*):ti,ab
#15.	((radiological* NEXT isolat*) NEXT syndrome*):ti,ab
#16.	MeSH descriptor: [Optic Neuritis] explode all trees
#17.	((neuromyelitis or neuritis or neuropapillitis) NEXT (retrobulbar or optic*)):ti,ab
#18.	(NMO or NMOSD):ti,ab
#19.	(OR #1-#18)
#20.	MeSH descriptor: [Aspirin] explode all trees

#21.	(Aspirin or Acetylsalicylic acid or ASA or Acetysal or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin or Acetyloxy benzoic Acid):ti,ab
#22.	MeSH descriptor: [Amantadine] explode all trees
#23.	(Amantadin* or Lysovir or Symmetrel or Aman or merz or ratiopharm or neuraxpharm or amantahciazu or amanta or mantadix or cerebramed or amantadinratiopharm or tregor or midantan or pmsamantadine or wiregyt or "1 aminoadamantane" or ratiopharm or azupharma or amantasulfateazu or adamantylamine or endantadine or symadine or genamantadine or amixx or adekin or viregyt or gen-amantadine or infex):ti,ab
#24.	MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees
#25.	MeSH descriptor: [Citalopram] explode all trees
#26.	MeSH descriptor: [Paroxetine] explode all trees
#27.	MeSH descriptor: [Fluoxetine] explode all trees
#28.	MeSH descriptor: [Modafinil] explode all trees
#29.	(SSRI* or Citalopram or Cytalopram or Cipramil or Cipralex or Lexapro or escitalopram or Fluoxetine or Prozac or oxactin or prozit or Fluvoxamine or Faverin or sarafem or Paroxetine or Seroxat or Sertraline or Lustral or paxil or aropax or modafanil or Armodafanil or Buproprion or Methylphenadite or Dextroamphetamine or Zolpidem or Venlafaxine):ti,ab
#30.	((serotonin or inhibitor) near/2 (uptake or reuptake)):ti,ab
#31.	MeSH descriptor: [Vitamin B 12] explode all trees
#32.	MeSH descriptor: [Hydroxocobalamin] explode all trees
#33.	(((B-12 or B12) near/1 vitamin) or cyanocobalamin or cobamide* or cobalamin* or eritron or cytamen or hydroxycobalamin):ti,ab
#34.	(or #20-#33)
#35.	#19 and #34
#36.	conference:pt or (clinicaltrials or trialsearch):so
#37.	#35 not #36

Epistemonikos search terms

1.	(((advanced_title_en:(multiple sclerosis) OR advanced_abstract_en:(multiple sclerosis)) AND (advanced_title_en:(aspirin OR Amantadine OR Serotonin OR Citalopram OR Paroxetine OR fluoxetine OR Modafinil OR Vitamin B 12 OR Hydroxocobalamin) OR advanced_abstract_en:(aspirin OR Amantadine OR Serotonin OR Citalopram OR Paroxetine OR fluoxetine OR Modafinil OR Vitamin B 12 OR Hydroxocobalamin)))

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 18: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies

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

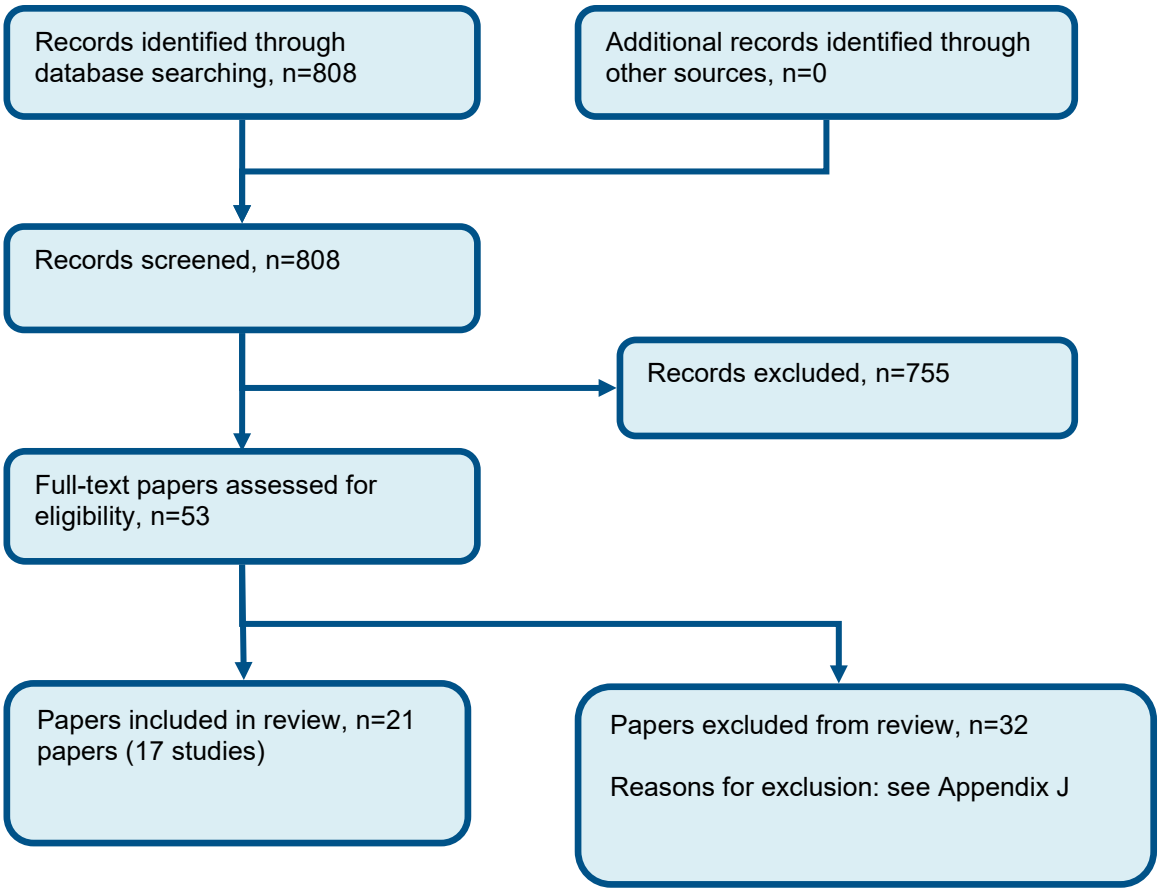
#1.	MeSH DESCRIPTOR Multiple Sclerosis EXPLODE ALL TREES
#2.	(((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	(MS)
#5.	MeSH DESCRIPTOR Myelitis, Transverse EXPLODE ALL TREES
#6.	(transverse myelitis)
#7.	MeSH DESCRIPTOR Demyelinating Diseases EXPLODE ALL TREES
#8.	((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 the pharmacological management of fatigue in people with multiple sclerosis



Appendix D – Effectiveness evidence

Anonymous, 1987

Bibliographic Reference	Anonymous; A randomized controlled trial of amantadine in fatigue associated with multiple sclerosis; Canadian journal of neurological sciences; 1987; vol. 14 (no. 3); 273-278

Study details

Secondary publication of another included study- see primary study for details	**No additional information.**
Other publications associated with this study included in review	No additional information.
Trial name / registration number	Trial by the Canadian MS Research Group.
Study location	Canada.
Study setting	Eleven multiple sclerosis research clinics.
Study dates	No additional information.
Sources of funding	This study was supported by a grant from Du Pont Pharmaceuticals.
Inclusion criteria	At least a 6-month history of definite multiple sclerosis according to the Schumacher criteria; at least a 3-month history of chronic, persistent, moderate to severe, daily fatigue.
Exclusion criteria	Pregnancy; hypersensitivity to amantadine; congestive heart failure or peripheral oedema; hepatic or renal impairment; epilepsy; history of depression or other psychiatric disorders; acute anaemia; thyroid disorders; diabetes; gastric or duodenal ulcers; alcohol or drug abuse.
Recruitment / selection of participants	No additional information.

Secondary publication of another included study- see primary study for details	**No additional information.**
Intervention(s)	Amantadine 100mg orally twice a day for 3 weeks (with a 2-week washout period before the study, and a 2-week washout period before crossing over to placebo treatment for 3 weeks). Concomitant therapy: The only concomitant medications permitted were small doses of muscle relaxants (baclofen, dantrolene) to control spasticity; anticholinergics (oxybutynin) for bladder control; and short-acting benzodiazepines at bedtime.
Comparator	Placebo twice a day orally for 3 weeks (with a 2-week washout period before the study, and a 2-week washout period before crossing over to amantadine 100mg twice a day treatment for 3 weeks). Concomitant therapy: The only concomitant medications permitted were small doses of muscle relaxants (baclofen, dantrolene) to control spasticity; anticholinergics (oxybutynin) for bladder control; and short-acting benzodiazepines at bedtime.
Number of participants	115 (crossover trial).
Duration of follow-up	10 weeks in total (3 weeks on either treatment arm).
Additional comments	Subgroup information: Type of MS - See participant characteristics table. Mixed. EDSS score - See participant characteristics table. <6. Disease modifying treatment status - Not stated/unclear Drug doses - Standard dose Routes of administration - Oral People receiving palliative care - Not stated/unclear

Study arms

Amantadine (N = 115)

Amantadine 100mg orally twice a day for 3 weeks (in a crossover study with a two-week washout period before the study and between the treatments)

Placebo (N = 115)

Matching placebo orally twice a day for 3 weeks (in a crossover study with a two-week washout period before the study and between the treatments)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 115)**
% Female Sample size	n = 76 ; % = 66
Mean age (SD) (years) Reported mean age (standard error) Mean (SE)	40.8 (1)
Ethnicity Custom value	NA
Comorbidities Custom value	NA
Relapsing-remitting Sample size	n = 57 ; % = 50
Relapsing/progressing Sample size	n = 33 ; % = 29

Characteristic	Study (N = 115)
Chronic progressing Sample size	n = 22 ; % = 19
Benign Sample size	n = 3 ; % = 3
EDSS score (mean [SE]) Mean (SE)	4.2 (0.2)
Duration of MS (mean [SE]) (years) Mean (SE)	7.8 (0.6)
Duration of fatigue (mean [SE]) (years) Mean (SE)	4.2 (0.4)

Outcomes

Study timepoints

- 3 week

Amantadine compared to placebo at 3-6 months (3 weeks) - dichotomous outcomes

Outcome	Amantadine, 3-week, N = 115	Placebo, 3-week, N = 115
Disruption of sleep (Insomnia) Dichotomous outcome, adverse event	n = 34 ; % = 29.6	n = 19 ; % = 16.5

Outcome	Amantadine, 3-week, N = 115	Placebo, 3-week, N = 115
No of events		
Cardiac events/arrhythmias (congestive heart failure) Dichotomous outcome, adverse event No of events	n = 0 ; % = 0	n = 0 ; % = 0
Adverse events leading to withdrawal Dichotomous outcome, adverse event No of events	n = 2 ; % = 1.7	n = 4 ; % = 3.5

Data taken from Amantadine treatment 3 weeks and Placebo treatment 3 weeks categories. Due to duration of studies being <3 months, will be included by downgraded for indirectness.

Amantadine compared to placebo at 3-6 months (3 weeks) - continuous outcomes (final values)

Outcome	Amantadine, 3-week, N = 86	Placebo, 3-week, N = 86
Psychological symptoms (Beck Depression Inventory, 21 item version) Mean (SE) - extracted from body of text. Scale range: 0-63. Mean (SE)	7.34 (0.81)	7.59 (0.84)
Cognitive functions (13-item activities of daily living, intellectual function factor [5 items] Measured on a 50mm VAS with the mean from all measures in the category being used. Mean (SE)	7.67 (0.35)	8.25 (0.34)

Psychological symptoms (Beck Depression Inventory, 21 item version) - Polarity - Lower values are better

Cognitive functions (13-item activities of daily living, intellectual function factor [5 items] - Polarity - Lower values are better

Data taken from Amantadine treatment 3 weeks and Placebo treatment 3 weeks categories. Due to duration of studies being <3 months, will be included by downgraded for indirectness.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Disruption of sleep (Insomnia)-Amantadine-Placebo-3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness due to short follow up period (<3 months))*

Cardiac events/arrhythmias (congestive heart failure)-Amantadine-Placebo-3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness due to short follow up period (<3 months))*

Adverse events leading to withdrawal-Amantadine-Placebo-3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
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	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness due to short follow up period (<3 months))*

Psychological symptoms (Beck Depression Inventory, 21 item version)-Amantadine-Placebo-3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Indirectly applicable *(Outcome indirectness due to short follow up period (<3 months))*

Cognitive functions (13-item activities of daily living, intellectual function factor [5 items]-Amantadine-Placebo-3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness due to short follow up period (<3 months))*

Ashtari, 2009

Bibliographic Reference	Ashtari, F.; Fatehi, F.; Shaygannejad, V.; Chitsaz, A.; Does amantadine have favourable effects on fatigue in Persian patients suffering from multiple sclerosis?; Neurologia i neurochirurgia polska; 2009; vol. 43 (no. 5); 428-432

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Iran.
Study setting	The MS Clinic affiliated to Isfahan University of Medical Sciences.

Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Diagnosis of clinically definite relapsing-remitting MS according to McDonald's criteria, age of patients between 18 and 50, Fatigue Severity Scale score more than 4.5, and Expanded Disability Status Scale (EDSS) less than 4.5.
Exclusion criteria	People with symptoms of depression according to DSM-IV criteria or any medical condition other than MS.
Recruitment / selection of participants	No additional information.
Intervention(s)	Oral amantadine 200mg per day for 2 months. Concomitant treatment: No additional information.
Comparator	Oral placebo for 2 months. Concomitant treatment: No additional information.
Number of participants	42 (21 in each study arm).
Duration of follow-up	2 months.
Additional comments	Subgroup categories: Type of MS: Relapsing-remitting MS.

	EDSS: See participants characteristics table. <6. Disease-modifying treatment: All were receiving treatment with disease modifying agents (either interferon-beta, cytotoxic drugs or a combination of both). Drug doses: Standard dose. Route of administration: Oral. People receiving palliative care: Not stated/unclear. The study reports adverse events in the amantadine group but do not explicitly state if there are adverse events in the placebo group. Therefore, this data was not extracted.

Study arms

Amantadine (N = 21)

Oral amantadine 200mg per day for 2 months

Placebo (N = 21)

Oral placebo for 2 months

Characteristics

Arm-level characteristics

Characteristic	Amantadine (N = 21)	Placebo (N = 21)
% Female Sample size	n = 7 ; % = 33.3	n = 4 ; % = 19
Mean age (SD) Mean (SD)	26.05 (5.95)	24.91 (4.04)
Persian race, Caucasian ethnicity Sample size	n = 21 ; % = 100	n = 21 ; % = 100
Comorbidities Nominal	NR	NR
EDSS score Mean (SD)	2.07 (0.78)	3.04 (5.09)
Disease duration (years) Mean (SD)	5.81 (2.3)	5.53 (2.14)
FSS score Scale range: 1-7 (mean of all questions). Lower values are better. Mean (SD)	5.27 (1.11)	4.89 (1.13)

Outcomes

Study timepoints

- 2 month (Will be classified as 3-6 months. However, all outcomes will be downgraded for indirectness due to short follow up period (<3 months).)

Amantadine compared to placebo at 3-6 months - continuous outcomes (change score)

Outcome	Amantadine, 2-month, N = 21	Placebo, 2-month, N = 21
Patient-reported outcome measures to assess MS fatigue (FSS) Scale range: 1-7. Mean (SD)	-1.27 (0.53)	-0.66 (0.33)

Patient-reported outcome measures to assess MS fatigue (FSS) - Polarity - Lower values are better

Will be classified as 3-6 months. However, all outcomes will be downgraded for indirectness due to short follow up period (<3 months). Reports final value and change score, change score used as the values for baseline data were different between groups.

Amantadine compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Amantadine, 2-month, N = 21	Placebo, 2-month, N = 21
Withdrawal due to adverse events Adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0

Will be classified as 3-6 months. However, all outcomes will be downgraded for indirectness due to short follow up period (<3 months).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(changescore)-Patient-reportedoutcomemeasurestoassessMSfatigue(FSS)-MeanSD-Amantadine-Placebo-t2

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 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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Differences in baseline values unlikely to have*

Section	Question	Answer
		an effect on this outcome. Seems harsh to downgrade it twice.)
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 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period (<3 months))*

Cambron, 2016

Bibliographic Reference	Cambron, M.; Mostert, J.; Parra, J.; D'Hooghe, M.; Nagels, G.; Willekens, B.; Heersema, D.; Debruyne, J.; Van Hecke, W.; Algoed, L.; De Klippel, N.; Fosselle, E.; Laureys, G.; Merckx, H.; Van Wijmeersch, B.; Vanopdenbosch, L.; Verhaegen, W.; Hupperts, R.; Hengstman, G.; Michiels, V.; Van Merhaegen-Wieleman, A.; De Keyser, J.; Fluoxetine in progressive multiple sclerosis (FLUOX-PMS); Multiple Sclerosis; 2016; vol. 22 (no. supplement3); 832-833

Study details

Secondary publication of another included study- see primary study for details	Cambron, Melissa; Mostert, Jop; D'Hooghe, Marie; Nagels, Guy; Willekens, Barbara; Debruyne, Jan; Algoed, Luc; Verhagen, Wim; Hupperts, Raymond; Heersema, Dorothea; De Keyser, Jacques; Group, Fluox-Pms Study; Fluoxetine in progressive multiple sclerosis: The FLUOX-PMS trial; Multiple sclerosis (Houndmills, Basingstoke, England); 2019; vol. 25 (no. 13); 1728-1735

Cambron, 2019

Bibliographic Reference	Cambron, Melissa; Mostert, Jop; D'Hooghe, Marie; Nagels, Guy; Willekens, Barbara; Debruyne, Jan; Algoed, Luc; Verhagen, Wim; Hupperts, Raymond; Heersema, Dorothea; De Keyser, Jacques; Group, Fluox-Pms Study; Fluoxetine in progressive multiple sclerosis: The FLUOX-PMS trial; Multiple sclerosis (Houndmills, Basingstoke, England); 2019; vol. 25 (no. 13); 1728-1735

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	Cambron, M.; Mostert, J.; Parra, J.; D'Hooghe, M.; Nagels, G.; Willekens, B.; Heersema, D.; Debruyne, J.; Van Hecke, W.; Algoed, L.; De Klippel, N.; Fosselle, E.; Laureys, G.; Merckx, H.; Van Wijmeersch, B.; Vanopdenbosch, L.; Verhaegen, W.; Hupperts, R.; Hengstman, G.; Michiels, V.; Van Merhaegen-Wieleman, A.; De Keyser, J.; Fluoxetine in progressive multiple sclerosis (FLUOX-PMS); Multiple Sclerosis; 2016; vol. 22 (no. supplement3); 832-833
Trial name / registration number	FLUOX-PMS trial. EudraCT Number 2011-003775-11.

Study location	Belgium, The Netherlands
Study setting	Multicenter trial. The majority of the study was conducted in the individual's home.
Study dates	Between February 2012 and March 2016
Sources of funding	The study was funded by IWT (Agentschap voor Innovatie door Wetenschap en Technologie, Belgium; TBM-IWT project 100772); additional financial support for the Dutch participants was provided by MS Anders (Amsterdam, the Netherlands)
Inclusion criteria	People with either secondary progressive multiple sclerosis or primary progressive multiple sclerosis, aged 25-65 years with a score on the Expanded Disability Status Scale (EDSS) of 3-6.5, and documented confirmed evidence of disease progression independent of relapse over the year prior to enrolment, defined as an increase of at least 0.5 points on the EDSS, were enrolled.
Exclusion criteria	Use of antidepressants; pregnancy or lactations; other neurologic or psychiatric disorders (including major depression) or systemic disorders that could interfere with the assessments. For sexually active female patients with reproductive potential, use of reliable means of contraception was required.
Recruitment / selection of participants	No additional information.
Intervention(s)	Fluoxetine 20mg orally for 4 weeks, followed by a daily single intake of 2 tablets of 20mg fluoxetine until week 108 Concomitant medications that could lead to clinically significant interactions with fluoxetine (such as monoamine oxidase inhibitors) were not allowed. The use of interferon beta or glatiramer acetate was allowed, as these drugs are ineffective in slowing down disability accrual in progressive MS. Patients using other immunosuppressive or immunomodulatory drugs could only be included if the drug was stopped at least for 2 months before randomisation.
Comparator	A placebo tablet orally for 4 weeks, followed by a daily single intake of 2 tablets of placebo until week 108 Concomitant medications that could lead to clinically significant interactions with fluoxetine (such as monoamine oxidase inhibitors) were not allowed. The use of interferon beta or glatiramer acetate was allowed, as these drugs are ineffective in slowing down disability accrual in progressive MS. Patients using other immunosuppressive or immunomodulatory drugs could only be included if the drug was stopped at least for 2 months before randomisation.
Number of participants	151 (74 assigned fluoxetine, 77 assigned placebo)

Duration of follow-up	108 weeks (2 years)
Additional comments	Subgroup details: Type of MS: See participant characteristics table EDSS: See participant characteristics table. <6. Disease modifying treatment status: People were allowed to use some treatment (see concomitant therapies). However, only around 27% received them (see baseline characteristics table). Drug doses: Standard dose Routes of administration: Oral People receiving palliative care: Not stated/unclear Note: For participant characteristics table, they only report baseline values for people included in the primary efficacy analysis (Fluoxetine = 69, placebo = 68)

Study arms

Fluoxetine (N = 74)

Fluoxetine 20mg orally for 4 weeks, followed by a daily single intake of 2 tablets of 20mg fluoxetine until week 108

Placebo (N = 77)

A placebo tablet orally for 4 weeks, followed by a daily single intake of 2 tablets of placebo until week 108

Characteristics

Arm-level characteristics

Characteristic	Fluoxetine (N = 74)	Placebo (N = 77)
% Female Sample size	n = 31 ; % = 44.9	n = 30 ; % = 44.1
Mean age (SD) Mean (SD)	54 (6.11)	51.2 (7.64)
Ethnicity Sample size	n = NA	n = NA
Comorbidities Sample size	n = NA	n = NA
Primary progressive MS Sample size	n = 40 ; % = 58	n = 37 ; % = 54.4
Secondary progressive MS Sample size	n = 27 ; % = 39.1	n = 28 ; % = 41.2
EDSS	5.1 (1.25)	5.2 (1.36)

Characteristic	Fluoxetine (N = 74)	Placebo (N = 77)
Mean (SD)		
Disease-modifying treatment Sample size	n = 18 ; % = 26.1	n = 19 ; % = 27.9
Disease duration (years) Mean (SD)	14.4 (8.79)	12.2 (7.87)
Beck Depression Inventory-II Lower is better Mean (SD)	14.7 (10.07)	11.3 (6.43)
Symbol digit modalities test Lower is better Mean (SD)	36.2 (11.07)	37.6 (11.39)
California Verbal Learning Test-II High is better Mean (SD)	128.8 (30.75)	131.7 (25.59)
Controlled Oral Word Association semantic High is better Mean (SD)	20.2 (5.95)	20.5 (6.44)
Controlled Oral Word Association phonetic High is better Mean (SD)	30.1 (13.6)	30.1 (16.87)

Characteristic	Fluoxetine (N = 74)	Placebo (N = 77)
Modified fatigue impact scale Lower is better Mean (SD)	40.3 (19.29)	40.1 (13.24)

Outcomes

Study timepoints

- 60 week (Slightly over a year, not the study endpoint (endpoint = 108 weeks). This is similar to 1 year of follow up, and so will be included in the >6 months-1 year group and will not be downgraded for indirectness due to the value being close to the same (and that the person will not have been receiving the target dose for fluoxetine until 4 weeks after the study starts).)

SSRI compared to placebo at 6-12 months - continuous outcomes (final values)

Outcome	Fluoxetine, 60-week, N = 68	Placebo, 60-week, N = 66
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) Scale range: 0-84 Mean (SD)	39.5 (16.1)	35 (17.4)
Psychological symptoms (Beck Depression Inventory-II) Scale range: 0-63 Mean (SD)	11.9 (8.6)	11.3 (7.3)

Outcome	Fluoxetine, 60-week, N = 68	Placebo, 60-week, N = 66
Cognitive functions (symbol digit modalities test) Outcome shows the number of numbers paired with figures in 90 seconds Mean (SD)	35.9 (11.4)	37 (12.1)
Cognitive functions (California Verbal Learning Test-II) The number of nouns that can be recalled when requested Mean (SD)	137.5 (28.8)	137 (27.2)
Cognitive functions (Controlled Oral Word Association Test - semantic) The number of words named beginning with a letter, excluding proper nouns within 1 minute (repeated 3 times) Mean (SD)	20.4 (5.9)	20 (6.1)
Cognitive functions (Controlled Oral Word Association Test - phonetic) The number of words named beginning with a letter, excluding proper nouns within 1 minute (repeated 3 times) Mean (SD)	34.6 (12.8)	29.1 (10.5)

Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) - Polarity - Lower values are better

Psychological symptoms (Beck Depression Inventory-II) - Polarity - Lower values are better

Cognitive functions (symbol digit modalities test) - Polarity - Higher values are better

Cognitive functions (California Verbal Learning Test-II) - Polarity - Higher values are better

Cognitive functions (Controlled Oral Word Association Test - semantic) - Polarity - Higher values are better

Cognitive functions (Controlled Oral Word Association Test - phonetic) - Polarity - Higher values are better

In the paper, this will use values from week 60

SSRI compared to placebo at 6-12 months - dichotomous outcomes

Outcome	Fluoxetine, 60-week, N = 69	Placebo, 60-week, N = 68
Adverse events leading to withdrawal Dichotomous outcome, adverse event No of events	n = 5 ; % = 7.2	n = 7 ; % = 10.3
Disruption to sleep (insomnia) Dichotomous outcome, adverse event No of events	n = 1 ; % = 1.5	n = 0 ; % = 0

In the paper, this will use values from week 60

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

SSRI compared to placebo at 6-12months-continuous outcomes (final values)-Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale)-60 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat6-12months-continuousoutcomes(finalvalues)-Psychologicalsymptoms(BeckDepressionInventory-II)-MeanSD-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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

SSRIcomparedtoplaceboat6-12months-continuousoutcomes(finalvalues)-Cognitivefunctions(symboldigitmodalitiestest)-MeanSD-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat6-12months-continuousoutcomes(finalvalues)-Cognitivefunctions(CaliforniaVerbalLearningTest-II)-MeanSD-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat6-12months-continuousoutcomes(finalvalues)-Cognitivefunctions(ControlledOralWordAssociationTest-semantic)-MeanSD-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat6-12months-continuousoutcomes(finalvalues)-CognitivefunctionS(ControlledOralWordAssociationTest-phonetic)-MeanSD-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat6-12months-dichotomousoutcomes-Adverseeventsleadingtowithdrawal-NoOfEvents-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat6-12months-dichotomousoutcomes-Disruptiontosleep(insomnia)-NoOfEvents-Fluoxetine-Placebo-t60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Chataway, 2015

Bibliographic Reference	Chataway, J.; Chandran, S.; Miller, D.; Giovannoni, G.; Wheeler-Kingshott, C.; Pavitt, S.; Stallard, N.; Hawkins, C.; Sharrack, B.; The ms-smart trial in secondary progressive multiple sclerosis: A multi-arm, multi-centre trial of neuroprotection; Journal of Neurology, Neurosurgery and Psychiatry; 2015; vol. 86 (no. 11)

Study details

Secondary publication of another included study- see primary study for details	Chataway, Jeremy; De Angelis, Floriana; Connick, Peter; Parker, Richard A.; Plantone, Domenico; Doshi, Anisha; John, Nevin; Stutters, Jonathan; MacManus, David; Prados Carrasco, Ferran; Barkhof, Frederik; Ourselin, Sebastien; Braisher, Marie; Ross, Moira; Cranswick, Gina; Pavitt, Sue H.; Giovannoni, Gavin; Gandini Wheeler-Kingshott, Claudia Angela; Hawkins, Clive; Sharrack, Basil; Bastow, Roger; Weir, Christopher J.; Stallard, Nigel; Chandran, Siddharthan; Investigators, Ms-Smart; Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial; The Lancet. Neurology; 2020; vol. 19 (no. 3); 214-225

Chataway, 2020

Bibliographic Reference	Chataway, Jeremy; De Angelis, Floriana; Connick, Peter; Parker, Richard A.; Plantone, Domenico; Doshi, Anisha; John, Nevin; Stutters, Jonathan; MacManus, David; Prados Carrasco, Ferran; Barkhof, Frederik; Ourselin, Sebastien; Braisher,

Marie; Ross, Moira; Cranswick, Gina; Pavitt, Sue H.; Giovannoni, Gavin; Gandini Wheeler-Kingshott, Claudia Angela; Hawkins, Clive; Sharrack, Basil; Bastow, Roger; Weir, Christopher J.; Stallard, Nigel; Chandran, Siddharthan; Investigators, Ms-Smart; Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial; The Lancet. Neurology; 2020; vol. 19 (no. 3); 214-225

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	Chataway, J.; Chandran, S.; Miller, D.; Giovannoni, G.; Wheeler-Kingshott, C.; Pavitt, S.; Stallard, N.; Hawkins, C.; Sharrack, B.; The ms-smart trial in secondary progressive multiple sclerosis: A multi-arm, multi-centre trial of neuroprotection; Journal of Neurology, Neurosurgery and Psychiatry; 2015; vol. 86 (no. 11)
Trial name / registration number	MS-SMART. ClinicialTrials.gov registry = NCT01910259.
Study location	United Kingdom.
Study setting	People from 13 clinical neuroscience centres in the UK.
Study dates	December 2014 to July 2018.
Sources of funding	Funded by Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership, UK Multiple Sclerosis Society, and US National Multiple Sclerosis Society.
Inclusion criteria	People aged 25-65 years with a diagnosis of secondary progressive multiple sclerosis, confirmed as per usual clinical practice. An Expanded Disability Status Scale (EDSS) score between 4.0 and 6.5, evidence of steady disability progression in the preceding 2 years (with either an increase of at least 1 point in EDSS score or a clinically documented increase in disability), and no concurrent use of disease-modifying therapies (standard UK practice for people with secondary progressive multiple sclerosis).

Exclusion criteria	People were ineligible for the study if they had primary progressive multiple sclerosis; significant depression (Beck's Depression Index II score >19); major comorbidity, glaucoma or epilepsy; were not able to undertake MRI; had a relapse or had been treated with corticosteroids within 3 months of screening; or used immunosuppressants, disease-modifying treatments, or experimental drugs within the previous 6 or 12 months (depending on the agent).
Recruitment / selection of participants	People recruited from neuroscience centres.
Intervention(s)	1) Amiloride hydrochloride 5mg orally once a day for 4 weeks, then twice a day from week 4 to week 96. (This group is not included in the protocol for this review so data will not be extracted). 2) Fluoxetine 20mg orally once a day for 4 weeks, then twice a day from week 4 to week 96. 3) Riluzole 50mg orally once a day for 4 weeks, then twice a day from week 4 to week 96. (This group is not included in the protocol for this review so data will not be extracted). Concomitant therapy: No additional information.
Comparator	Placebo orally once a day for 4 weeks, then twice a day from week 4 to week 96. Concomitant therapy: No additional information.
Number of participants	445 (111 allocated to amiloride, 111 allocated to fluoxetine, 111 allocated to riluzole, 112 allocated to placebo).
Duration of follow-up	96 weeks.
Additional comments	Subgroup information: Type of multiple sclerosis: Secondary progressive multiple sclerosis

	EDSS score: See participant characteristics table. ≥6. Disease modifying treatment status: Not stated/unclear. Drug doses: Standard doses. Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Fluoxetine (N = 111)

Fluoxetine 20mg orally once a day for 4 weeks, then twice a day from week 4 to week 96.

Placebo (N = 112)

Placebo orally once a day for 4 weeks, then twice a day from week 4 to week 96.

Characteristics

Arm-level characteristics

Characteristic	Fluoxetine (N = 111)	Placebo (N = 112)
% Female Sample size	n = 74 ; % = 67	n = 75 ; % = 67

Characteristic	Fluoxetine (N = 111)	Placebo (N = 112)
Mean age (SD) Range	NA to NA	NA to NA
Mean age (SD) Mean (SD)	NA (NA)	NA (NA)
Mean age (SD) Median (IQR)	55.5 (50.7 to 60.2)	56.4 (49.2 to 60.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Comorbidities No of events	n = NA ; % = NA	n = NA ; % = NA
EDSS score Expanded Disability Status Scale score Range	NA to NA	NA to NA
EDSS score Expanded Disability Status Scale score Mean (SD)	NA (NA)	NA (NA)
EDSS score Expanded Disability Status Scale score Median (IQR)	6 (5.5 to 6.5)	6 (5.5 to 6.5)

Characteristic	Fluoxetine (N = 111)	Placebo (N = 112)
Time since first symptoms (years) Range	NA to NA	NA to NA
Time since first symptoms (years) Mean (SD)	NA (NA)	NA (NA)
Time since first symptoms (years) Median (IQR)	21 (16 to 29)	19 (13 to 29)
Beck Depression Index II score Median (IQR)	6 (3 to 10)	7 (4 to 12)
Symbol digit modalities test Mean (SD)	44.1 (11.4)	44.1 (12.8)
EQ-5D-5L utility index score Mean (SD)	0.7 (0.16)	0.67 (0.18)
EQ-5D-5L visual analogue scale score Mean (SD)	67.5 (19.5)	65.2 (20.3)
Neurological Fatigue Index Summary Score Mean (SD)	17.4 (3.9)	17.8 (3.9)

Outcomes

Study timepoints

- 96 week (This group is data from >1 year by a substantial amount. This group will only be used for the extraction of dichotomous outcomes as there is continuous data reported at 48 weeks in the appendix.)
- 48 week (This data is reported in the appendix for the document. Values will be extracted from this information.)

SSRI compared to placebo at >6 months - 1 year - continuous data (final values)

Outcome	Fluoxetine, 96-week, N = NA	Fluoxetine, 48-week, N = 93	Placebo, 96-week, N = NA	Placebo, 48-week, N = 101
Patient-reported outcome measures to assess MS fatigue (Neurological Fatigue Index Summary Score) Scale range: 0-30 Mean (SD)	NA (NA)	17.87 (3.69)	NA (NA)	18.2 (4.25)
Health-related Quality of Life (EQ-5D-5L utility index score) Scale range: -0.11-1 Mean (SD)	NA (NA)	0.66 (0.17)	NA (NA)	0.65 (0.19)
Health-related Quality of Life (EQ-5D-5L visual analogue scale score) Scale range: 0-100 Mean (SD)	NA (NA)	66.14 (18.58)	NA (NA)	62.96 (22.43)
Cognitive functions (symbol digit modalities test) (Number of correct answers) Mean (SD)	NA (NA)	44.45 (12.18)	NA (NA)	44.96 (13.09)

Patient-reported outcome measures to assess MS fatigue (Neurological Fatigue Index Summary Score) - Polarity - Higher values are better

Health-related Quality of Life (EQ-5D-5L utility index score) - Polarity - Higher values are better

Health-related Quality of Life (EQ-5D-5L visual analogue scale score) - Polarity - Higher values are better

Cognitive functions (symbol digit modalities test) - Polarity - Higher values are better

Using data at 48 weeks.

SSRI compared to placebo at >6 months - 1 year - dichotomous data

Outcome	Fluoxetine, 96-week, N = 111	Fluoxetine, 48-week, N = NA	Placebo, 96-week, N = 112	Placebo, 48-week, N = NA
Cardiac events/arrhythmias (cardiac disorders in people xperiencing at least one adverse event) No of events	n = 3 ; % = 3	n = NA ; % = NA	n = 2 ; % = 2	n = NA ; % = NA

Using data at 96 weeks. These outcomes will be downgraded for indirectness due to the outcome being at >1 year.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

SSRIcomparedtoplaceboat>6months-1year-continuousdata(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(NeurologicalFatigueIndexSummaryScore)-MeanSD-Fluoxetine-Placebo-t48

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
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 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	Low
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat>6months-1year-continuousdata(finalvalues)-Health-relatedQualityofLife(EQ-5D-5Lutilityindexscore)-MeanSD-Fluoxetine-Placebo-t48

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat>6months-1year-continuousdata(finalvalues)-Health-relatedQualityofLife(EQ-5D-5Lvisualanaloguescalescore)-MeanSD-Fluoxetine-Placebo-t48

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 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	Low
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat>6months-1year-continuousdata(finalvalues)-Cognitivefunctions(symboldigitmodalitiestest)-MeanSD-Fluoxetine-Placebo-t48

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 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	Low
Overall bias and Directness	Overall Directness	Directly applicable

SSRIcomparedtoplaceboat>6months-1year-dichotomousdata-Cardiacevents/arrhythmias(cardiacdisordersinpeoplexperiencingatleastoneadverseevent)-NoOfEvents-Fluoxetine-Placebo-t96

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded as time period of outcome is >1 year)*

Cohen, 1989

Bibliographic Reference	Cohen, R. A.; Fisher, M.; Amantadine treatment of fatigue associated with multiple sclerosis; Archives of neurology; 1989; vol. 46 (no. 6); 676-680

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.

Trial name / registration number	No additional information.
Study location	United States of America.
Study setting	Study conducted at the Department of Neurology, University of Massachusetts Medical School and Worcester Memorial Hospital, Worcester, Mass.
Study dates	No additional information.
Sources of funding	This project was supported by a grant from Du Pont Pharmaceuticals, Wilmington, Del.
Inclusion criteria	People satisfying criteria for a definite/probable diagnosis of multiple sclerosis by the criteria of Poser et al. The diagnosis was established at least 6 months before patients entered the study. All people had daily symptomatic fatigue for at least 3 months.
Exclusion criteria	Depression; pregnancy; congestive heart failure; renal or hepatic impairment; epilepsy; anaemia; thyroid disorders; diabetes mellitus; active gastric or duodenal ulcer; psychiatric disorder; alcohol or drug abuse; people taking any of the following medications: stimulants, sedative-hypnotics, antidepressants, major tranquilizers, beta-blockers, immunosuppressants and steroids; Kurtzke rating of greater than 6.
Recruitment / selection of participants	No additional information.
Intervention(s)	Amantadine 100mg orally twice a day for 4 weeks.
Comparator	Crossover to placebo twice a day for 4 weeks.
Number of participants	29.
Duration of follow-up	10 weeks (2-week crossover)
Additional comments	Subgroup information: Type of multiple sclerosis: 13 were demonstrating a chronic deteriorating or relapsing/deteriorating course of illness, while 16 exhibited either a benign or remitting/relapsing course.

	EDSS score - people with a score >6 were excluded. Therefore <6. Disease modifying treatment status - no additional information Drug doses - standard dose Routes of administration - oral People receiving palliative care - Not stated/unclear No baseline values of outcomes are reported. The study reported cognitive function outcomes but do not report any values to calculate standard deviations from so these will not be extracted.

Study arms

Amantadine (N = 29)

Amantadine hydrochloride 100mg orally twice daily for 4 weeks (then crossed over to placebo twice daily orally for 4 weeks)

Placebo (N = 29)

Placebo orally twice daily for 4 weeks (then crossed over to amantadine hydrochloride 100mg twice daily orally for 4 weeks)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 29)**
% Female Sample size	n = 17 ; % = 58.6
Mean age (SD) Mean (SD)	44.5 (9.3)
Ethnicity Nominal	NA
Comorbidities Nominal	NA
Duration of disease Nominal	NA
Duration of fatigue symptoms (years) Mean (SD)	5.6 (4.5)

Outcomes

Study timepoints

- 10 week (This group is <3 months and so will be included in the 3-6 months category. However, all outcomes will be downgraded for indirectness.)

Amantadine compared to placebo - continuous outcomes (final value)

Outcome	Amantadine, 10-week, N = 22	Placebo, 10-week, N = 22
Energy level Mean (SE)	3.04 (0.09)	2.76 (0.07)
Muscle strength Mean (SE)	2.94 (0.09)	2.75 (0.07)
Concentration/memory Mean (SE)	3.4 (0.09)	2.98 (0.08)
Motivation level Mean (SE)	3.16 (0.09)	2.98 (0.08)
Ability to finish task Mean (SE)	3.16 (0.09)	3.02 (0.08)
Ability to solve problem Mean (SE)	3.37 (0.1)	3.13 (0.09)
Wellbeing Mean (SE)	3.17 (0.08)	2.9 (0.06)

Patient-reported outcome measures to assess MS fatigue (Diary ratings of fatigue) - Polarity - Higher values are better

This group is <3 months and so will be included in the 3-6 months category. However, all outcomes will be downgraded for indirectness.

Amantadine compared to placebo - dichotomous outcomes

Outcome	Amantadine, 10-week, N = 29	Placebo, 10-week, N = 29
Withdrawal due to adverse events Adverse events. The four withdrawing while taking placebo reported: influenza-like illness (2), constipation (1), fear of myocardial infarction (1). The three withdrawing while on amantadine reported: flare up of MS symptoms (1), influenza-like illness (1), nausea and anxiety (1). No of events	n = 3 ; % = 10.3	n = 4 ; % = 13.8

This group is <3 months and so will be included in the 3-6 months category. However, all outcomes will be downgraded for indirectness.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-Energylevel-MeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-Musclestrength-MeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns

Section	Question	Answer
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	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-Concentration/memory-MeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-MotivationlevelMeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	**Overall Directness**	**Partially applicable** ***(Downgraded due to short study follow up (<3 months))***

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-Abilitytofinishtask-MeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-Abilitytosolveproblem-MeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Amantadinecomparedtoplacebo-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(Diaryratingsoffatigue)-Wellbeing-MeanSE-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Amantadinecomparedtoplacebo-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Amantadine-Placebo-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Rated high as the lack of baseline characteristics is concerning given they are reporting final values.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to short study follow up (<3 months))*

Ehde, 2008

Bibliographic Reference	Ehde, D. M.; Kraft, G. H.; Chwastiak, L.; Sullivan, M. D.; Gibbons, L. E.; Bombardier, C. H.; Wadhwani, R.; Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis; General hospital psychiatry; 2008; vol. 30 (no. 1); 40-48

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study location	United States of America.
Study setting	Outpatient follow up.
Study dates	No additional information.

Sources of funding	GlaxoSmithKline provided the study medications (placebo and active) but did not participate in study conceptualization, study design, data analyses or manuscript preparation.
Inclusion criteria	Age of at least 18 years; a diagnosis of multiple sclerosis as confirmed by a neurologist or an MS-specialized physiatrist; a diagnosis of major depressive disorder and/or dysthymia based on the Structured Clinical Interview for DSM-IV Axis I Disorders administered by one of two study psychiatrists.
Exclusion criteria	Had failed treatment with paroxetine in the past; were in psychotherapy; were taking psychotropic medications; were taking >50mg of amitriptyline or equivalent for pain or sleep; displayed imminent suicidal ideation necessitating immediate psychiatric intervention; were pregnant, nursing or not using an effective contraceptive method; had bipolar disorder or evidence of psychosis based on the SCID; had a diagnosis of alcohol and/or drug dependence based on the SCID; were participating in another Food and Drug Administration drug study; had used corticosteroids within the 2 weeks prior to study enrolment.
Recruitment / selection of participants	People were recruited from a variety of sources including: the Western MS Center at the University of Washington; advertisements and articles in local newspapers and MS newsletters; flyers sent to local neurologists' offices; regional MS support groups.
Intervention(s)	Paroxetine 10mg per day, up titrated to 20mg/day after 1 week (2 capsules) and then could be further up titrated a maximum of 40mg/day in subsequent weeks dependent on symptoms or down titrated due to adverse events.
Comparator	Matching placebo
Number of participants	42 (22 received paroxetine, 20 received placebo)
Duration of follow-up	4 months
Additional comments	Subgroup information: Type of MS: Not stated/unclear. EDSS score: See participant characteristics table. Mixed. Disease modifying treatment status: Not stated/unclear. Drug doses: Standard doses.

	Routes of administration: Oral. People receiving palliative care: Not stated/unclear. Note: Outcomes will be downgraded for population indirectness as participants were required to have major depressive disorder or dysthymia to be included in the study.

Study arms

Paroxetine (N = 22)

10mg/day orally titrated up to 40mg daily based on symptoms, response and side effects.

Placebo (N = 20)

Matching placebo.

Characteristics

Study-level characteristics

Characteristic	Study (N = 42)
% Female Sample size	n = 22 ; % = 52.4

Characteristic	Study (N = 42)
Mean age (SD) Mean (SD)	45 (10.1)
White Sample size	n = 36 ; % = 85.7
Asian or Pacific Islander Sample size	n = 3 ; % = 7.1
African American Sample size	n = 2 ; % = 4.8
Multiracial Sample size	n = 1 ; % = 2.4
Comorbidities Nominal	NA
Mild (0-4) Sample size	n = 22 ; % = 52.4
Moderate (4.5-6.5) Sample size	n = 16 ; % = 38.1
Severe (7-9.5) Sample size	n = 4 ; % = 9.5

Arm-level characteristics

Characteristic	Paroxetine (N = 22)	Placebo (N = 20)
MFIS score Whole score: 0-84. Psychosocial subscale: 0-8. Physical subscale: 0-36. Cognitive subscale: 0-40. Lower is better. Mean (SD)	57.2 (14.1)	56.7 (12.6)
MFIS psychosocial subscale Scale range: 0-8. Mean (SD)	5.8 (1.5)	5.2 (1.3)
MFIS physical subscale Scale range: 0-36. Mean (SD)	25 (6.8)	26 (6.1)
MFIS cognitive subscale Scale range: 0-40. Mean (SD)	26.5 (9.8)	25.6 (7.2)
HAM-D score Scale range: 0-50, lower is better Mean (SD)	17.2 (4.3)	19 (4.6)
SF-36 physical component summary Mean (SD)	40.8 (13.2)	36 (11.4)

Characteristic	Paroxetine (N = 22)	Placebo (N = 20)
SF-36 mental component summary Mean (SD)	32.3 (10.7)	35.6 (8.9)
PDQ (Perceived Deficits Questionnaire) Scale range: 0-100. Lower is better. Mean (SD)	40.4 (14.2)	44 (13.8)
PDQ attention, concentration Mean (SD)	11.8 (4.3)	11.9 (3.8)
PDQ retrospective memory Mean (SD)	10.2 (4.3)	11.4 (4.2)
PDQ prospective memory Mean (SD)	8.1 (3)	8.9 (2.8)
PDQ plan, organize Mean (SD)	11.3 (4)	11.9 (3.9)

Outcomes

Study timepoints

- 4 month

SSRI compared to placebo at 3-6 months - continuous outcomes (final values)

Outcome	Paroxetine, 4-month, N = 22	Placebo, 4-month, N = 20
Patient-reported outcome measures to assess MS fatigue (MFIS) Whole score: 0-84. Psychosocial subscale: 0-8. Physical subscale: 0-36. Cognitive subscale: 0-40. Lower is better. Mean (SD)	39.3 (14.8)	52.1 (18.3)
Psychosocial subscale Scale range: 0-8 Mean (SD)	3.4 (1.7)	4.8 (1.9)
Physical subscale Scale range: 0-36 Mean (SD)	19.5 (7.3)	23.1 (9.2)
Cognitive subscale Scale range: 0-40 Mean (SD)	16.2 (8.8)	23.7 (8.4)
SF-36 physical component summary Mean (SD)	36.4 (12.3)	35.5 (13.3)
SF-36 mental component summary Mean (SD)	48.4 (32.3)	42.5 (9.7)
Cognitive functions (PDQ) Scale range: 0-100. Lower is better. Mean (SD)	29.1 (13.2)	40.4 (12.6)

Outcome	Paroxetine, 4-month, N = 22	Placebo, 4-month, N = 20
PDQ attention, concentration Mean (SD)	8.1 (4.2)	11.8 (3.6)
PDQ retrospective memory Mean (SD)	7.7 (4.5)	9.7 (4.3)
PDQ prospective memory Mean (SD)	5.4 (3.2)	8 (2.4)
PDQ plan, organize Mean (SD)	8 (3.5)	11 (3.9)
Psychological symptoms (HAM-D) Scale range: 0-50. Lower is better. Mean (SD)	6.4 (3)	10.9 (5.7)

Patient-reported outcome measures to assess MS fatigue (MFIS) - Polarity - Lower values are better

Health-related Quality of Life (SF-36) - Polarity - Higher values are better

Cognitive functions (PDQ) - Polarity - Lower values are better

Psychological symptoms (HAM-D) - Polarity - Lower values are better

SSRI compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Paroxetine, 4-month, N = 22	Placebo, 4-month, N = 20
Withdrawal due to adverse events Adverse events No of events	n = 2 ; % = 9.1	n = 0 ; % = 0

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFIS)-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFIS)-Psychosocialsubscale-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFIS)-Physicalsubscale-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a*

Section	Question	Answer
		major depressive disorder prior to starting treatment)

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFIS)-Cognitivesubscale-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Health-relatedQualityofLife(SF-36)-SF-36physicalcomponentsummary-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Health-relatedQualityofLife(SF-36)-SF-36mentalcomponentsummary-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(PDQ)-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(PDQ)-PDQattention,concentration-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(PDQ)-PDQretrospectivememory-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(PDQ)-PDQprospectivememory-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(PDQ)-PDQplan,organize-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-PsychologicalsymptomsHAM-D-MeanSD-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

SSRIcomparedtoplaceboat3-6months-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Paroxetine-Placebo-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to participants being required to have a major depressive disorder prior to starting treatment)*

Ford-Johnson, 2016

Bibliographic Reference	Ford-Johnson, L.; DeLuca, J.; Zhang, J.; Elovic, E.; Lengenfelder, J.; Chiaravalloti, N. D.; Cognitive effects of modafinil in patients with multiple sclerosis: A clinical trial; Rehabilitation psychology; 2016; vol. 61 (no. 1); 82-91

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	Clinicaltrials.gov - NCT00142402.
Study location	United States of America.
Study setting	MS Clinics
Study dates	No additional information.
Sources of funding	The study was developed under a grant from the National Multiple Sclerosis Society, grant number PP0911 and partially supported by a fellowship training grant from the Department of Education, NIDRR grant number H133P090009.
Inclusion criteria	Diagnosis of multiple sclerosis, must understand English.
Exclusion criteria	Significant language comprehension deficits; age greater than 60; less than 1-month post most recent exacerbation; current treatment with corticosteroids; significant neurological history aside from MS (e.g., epilepsy, TBI); significant substance abuse history as documented by the MAST-27; significant psychiatric history (e.g., Schizophrenia, Bipolar Disorder, Major Depression); non-fluency in the English language.
Recruitment / selection of participants	People were recruited from MS Clinics in the Northern New Jersey Area. Additionally, participants were recruited through participation in previous studies in the Neuroscience and Neuropsychology Laboratory of Kessler Foundation.
Intervention(s)	Modafinil 200mg once a day orally for 2 weeks, followed by 1 week washout, then placebo once a day orally for 2 weeks.

	Concomitant therapy: No additional information
Comparator	Placebo once a day orally for 2 weeks, followed by 1 week washout, then modafinil 200mg once a day orally for 2 weeks. Concomitant therapy: No additional information
Number of participants	18 (9 in each group)
Duration of follow-up	5 weeks
Additional comments	Subgroup information: Type of multiple sclerosis: See participant characteristics table. EDSS score: See participant characteristics table. EDSS <6. Disease modifying treatment status: Majority using disease modifying treatment. 2 Avonex, 4 Copoxone, 3 Betaseron, 1 Rebif, 6 none. Drug doses: Standard doses. Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Modafinil (N = 18)

Modafinil 200mg once a day orally

Placebo (N = 18)

Placebo once a day orally

Characteristics

Study-level characteristics

Characteristic	Study (N = 16)
% Female No of events	n = 13 ; % = 81.5
Mean age (SD) Mean (SD)	42.44 (8.06)
Ethnicity Nominal	NA
Comorbidities Nominal	NA

Characteristic	Study (N = 16)
Relapsing-remitting No of events	n = 10 ; % = 62.5
Primary progressive No of events	n = 1 ; % = 6.25
Secondary progressive No of events	n = 3 ; % = 18.8
Progressive relapsing No of events	n = 0 ; % = 0
Unknown No of events	n = 2 ; % = 12.5
Years since diagnosis Mean (SD)	10 (7.2)
Expanded Disability Status Scale Mean (SD)	3.9 (2.2)

Arm-level characteristics

Characteristic	Modafinil (N = 18)	Placebo (N = 18)
Digit Vigilance Test total errors Lower is better. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	2.5 (2.27)	4.6 (1.82)
Weschler Adult Intelligence Scale-III Digit Span Total High is better. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	17.11 (6.23)	15.63 (1.92)
Weschler Adult Intelligence Scale-III Letter Number Sequencing High is better. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	10 (2.29)	9.88 (2.1)
Symbol digit modalities test (Number of correct responses within 90 seconds) High is good. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	52.78 (13.09)	40.25 (12.17)
California Verbal Learning Test - Second Edition High is good. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	52.44 (8.96)	48.63 (9.96)
Modified Fatigue Impact Scale Total Score Lower is better, scale range: 0-84. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	33.38 (16.73)	42.88 (13.95)

Characteristic	Modafinil (N = 18)	Placebo (N = 18)
Chicago Multiscale Depression Inventory Total Score Scale range unclear. Lower is better. Assessed in randomised groups (therefore number of participants are 9 on each arm) Mean (SD)	67.11 (16.74)	66.38 (14.23)
The State Trait Anxiety Inventory Scale range 0-60 (20 questions on a 4-point scale). Lower is better. Mean (SD)	28.33 (9.42)	28.13 (6.96)
Bodily pain Mean (SD)	7.57 (2.83)	7.57 (2.95)
General health Mean (SD)	17.31 (4.64)	17.11 (3.99)
Mental health Mean (SD)	26.11 (2.98)	24.28 (4.61)
Physical functioning Mean (SD)	21.78 (5.72)	15.43 (3.82)
Role physical Mean (SD)	7.22 (0.83)	4.57 (0.79)
Vitality scale Mean (SD)	16.11 (3.66)	12 (7.64)

Outcomes

Study timepoints

- 2 week (2 weeks for each treatment)

Modafinil compared to placebo at 3-6 months - continuous outcomes (final value)

Outcome	Modafinil, 2-week, N = 16	Placebo, 2-week, N = 16
Cognitive functions (Digit Vigilance Test total errors) Lower is better Mean (SD)	4.21 (4.3)	5.55 (4.51)
Cognitive functions (Weschler Adult Intelligence Scale-III Digit Span Total) High is better Mean (SD)	16.62 (4.6)	17.25 (4.98)
Cognitive functions (Weschler Adult Intelligence Scale-III Letter Number Sequencing) Mean (SD)	10.94 (3.79)	11 (3.2)
Cognitive functions (symbol digit modalities test) (Number of correct responses in 90 seconds) Mean (SD)	50.81 (12.93)	51.13 (15.08)
Cognitive functions (California Verbal Learning Test - Second Edition) Mean (SD)	50.19 (13.33)	52.75 (12.19)

Outcome	Modafinil, 2-week, N = 16	Placebo, 2-week, N = 16
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale Total Score) Lower is better, scale range: 0-84. Mean (SD)	35 (16.99)	36.5 (13.54)
Psychological symptoms (Chicago Multiscale Depression Inventory Total Score) Scale range unclear Mean (SD)	67.69 (20.01)	67.32 (17.84)
Psychological symptoms (The State Trait Anxiety Inventory) Scale range 0-60 (20 questions on a 4-point scale). Lower is better. Mean (SD)	28.06 (7.17)	29.56 (9)
Bodily pain Mean (SD)	7.65 (2.52)	8.36 (2.56)
General health Mean (SD)	16.5 (6.35)	17.83 (3.27)
Mental health Mean (SD)	25.56 (3.7)	25.43 (3.65)
Physical functioning Mean (SD)	19.25 (5.64)	19.75 (6.38)
Role physical Mean (SD)	6.62 (1.56)	7.37 (4.21)

Outcome	Modafinil, 2-week, N = 16	Placebo, 2-week, N = 16
Vitality scale Mean (SD)	16 (3.77)	15.43 (3.82)

Cognitive functions (Digit Vigilance Test total errors) - Polarity - Lower values are better

Cognitive functions (Weschler Adult Intelligence Scale-III Digit Span Total) - Polarity - Higher values are better

Cognitive functions (Weschler Adult Intelligence Scale-III Letter Number Sequencing) - Polarity - Higher values are better

Cognitive functions (symbol digit modalities test) - Polarity - Higher values are better

Cognitive functions (California Verbal Learning Test - Second Edition) - Polarity - Higher values are better

Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale Total Score) - Polarity - Lower values are better

Psychological symptoms (Chicago Multiscale Depression Inventory Total Score) - Polarity - Higher values are better

Psychological symptoms (The State Trait Anxiety Inventory) - Polarity - Lower values are better

Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory) - Polarity - Higher values are better

All outcomes will be downgraded for indirectness due to short follow up duration (2 weeks rather than 3-6 months). For this values reported in the study are combined to form group effect (Group 1 follow up 1 and group 2 follow up 2 are combined to determine the Modafinil effect. Group 1 follow up 2 and group 2 follow up 1 are combined to determine the placebo effect.

Modafinil compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Modafinil, 2-week, N = 18	Placebo, 2-week, N = 18
Withdrawal due to adverse events Stated that the even was unrelated to the study drug	n = 1 ; % = 5.6	n = 0 ; % = 0

Outcome	Modafinil, 2-week, N = 18	Placebo, 2-week, N = 18
No of events		

All outcomes will be downgraded for indirectness due to short follow up duration (2 weeks rather than 3-6 months).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-DigitVigilanceTesttotalerrors-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-WeschlerAdultIntelligenceScale-IIIDigitSpanTotal-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-WeschlerAdultIntelligenceScale-IIILetterNumberSequencing-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Section	Question	Answer
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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-SymboldigitmodalitiestestMeanSD-ModafinilPlacebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-CaliforniaVerbalLearningTest-SecondEdition-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-ModifiedFatigueImpactScaleTotalScore-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-ChicagoMultiscaleDepressionInventoryTotalScore-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-TheStateTraitAnxietyInventory-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-MultipleSclerosisQualityofLifeInventory-Bodilypain-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-MultipleSclerosisQualityofLifeInventory-Generalhealth-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Section	Question	Answer
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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-MultipleSclerosisQualityofLifeInventory-MentalhealthMeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-MultipleSclerosisQualityofLifeInventory-PhysicalfunctioningMeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-MultipleSclerosisQualityofLifeInventory-Rolephysical-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalue)-MultipleSclerosisQualityofLifeInventory-Vitalityscale-MeanSD-Modafinil-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Section	Question	Answer
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Modafinilcomparedtoplaceboat3-6months-dichotomousoutcomes-WithdrawalduetoadverseeventsNoOfEvents-ModafinilPlacebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short study follow up time)*

Geisler, 1996

Bibliographic Reference	Geisler, M. W.; Sliwinski, M.; Coyle, P. K.; Masur, D. M.; Doscher, C.; Krupp, L. B.; The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis; Archives of neurology; 1996; vol. 53 (no. 2); 185-188

Study details

Secondary publication of another included study- see primary study for details	Krupp, L. B.; Coyle, P. K.; Doscher, C.; Miller, A.; Cross, A. H.; Jandorf, L.; Halper, J.; Johnson, B.; Morgante, L.; Grimson, R.; Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo; Neurology; 1995; vol. 45 (no. 11); 1956-1961.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United States of America.
Study setting	Outpatient follow up conducted at the Stony Brook MS Comprehensive Care Center, Stony Brook, NY.
Study dates	No additional information.
Sources of funding	This study was supported in part by grant RG2149-A-! from the National Multiple Sclerosis Society, New York, NY, and grant A13156 from the National Institutes of Health, Bethesda, Md.
Inclusion criteria	Age range 18 to 50 years; clinically or laboratory definite MS based on the criteria of Poser et al; Fatigue Severity Scale score of 4.0 or greater; ambulatory with a Kurtzke's Expanded Disability Status Scale score of 6.5 or less.

Exclusion criteria	A Kurtzke Expanded Disability Status Scale score greater than 6.5; severe depression, as assessed with the Center for Epidemiologic Studies-Depression Scale (score >35); severe dementia (Mini-Mental State Examination score <15); current or recent MS relapse within 2 months of the study; and no recent or current use of fatigue-producing medication (e.g. tricyclic antidepressants and benzodiazepines).
Recruitment / selection of participants	Participants are a subset of participants from a larger trial (Krupp 1993).

Study arms

Amantadine (N = 16)

Amantadine 100mg twice a day for 6 weeks

Placebo (N = 16)

Placebo twice a day for 6 weeks

Hamzei-Moghaddam A, Sedighi B, Iranmanesh F, 2011

Bibliographic Reference	Hamzei-Moghaddam A, Sedighi B, Iranmanesh F AM; Therapeutic Effect of Co-Administration of Amantadine and Aspirin on Fatigue in Patients with Multiple Sclerosis: A Randomized Placebo-Controlled Double-Blind Study; Iranian Journal of Pharmacology and Therapeutics; 2011; vol. 10 (no. 2); 71-80

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	Iranian Randomised Clinical trial number: 201112208430N3.
Study type	Randomised controlled trial (RCT)
Study location	Iran.
Study setting	Shafa Hospital, Kerman, Iran.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	Men and women aged between 20 and 50 years and had an EDSS score of 6.0 or less. People with a baseline FSS score of 4.0 or more. Fatigue as a persistent problem for more than 2 months and subjects should have FSS score of 4.0 or more in the screening visit.
Exclusion criteria	People with current or recent (within 2 months) use of medications that might influence fatigue (benzodiazepines, imipramine, azathioprine, or cyclophosphamide) or the following medications were excluded: stimulants, sedative-hypnotics, major tranquilizers, beta-blockers, immunosuppressants, nonsteroidal anti-inflammatory drugs, steroids and IFN-beta. Other exclusion criteria were: pregnancy; congestive heart failure; renal or hepatic impairment; epilepsy; diabetes mellitus; active gastric or duodenal ulcer; psychiatric disorder; alcohol or drug abuse; major depression; asthma; narcolepsy; other pathology possibly contributing to fatigue such as anaemia or hypothyroidism and unwillingness to discontinue amantadine or aspirin treatment.

Recruitment / selection of participants	No additional information.
Intervention(s)	Amantadine 100mg and aspirin 500mg twice a day for 6 weeks.
Comparator	Amantadine 100mg and placebo twice a day for 6 weeks.
Number of participants	45 (21 amantadine and aspirin, 24 amantadine and placebo).
Duration of follow-up	6 weeks.
Additional comments	Subgroup categories: Type of MS: Relapsing-remitting: 36. Secondary progressive: 9. EDSS: See participant characteristics table. Majority <6. Disease modifying treatment status: Not stated/unclear. Drug doses: Standard doses. Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Amantadine and aspirin (N = 21)

Amantadine 100mg and aspirin 500mg orally twice daily for 6 weeks

Amantadine and placebo (N = 24)

Amantadine 100mg and placebo orally twice daily for 6 weeks

Characteristics

Arm-level characteristics

Characteristic	Amantadine and aspirin (N = 21)	Amantadine and placebo (N = 24)
% Female No of events	n = 16 ; % = 76.2	n = 22 ; % = 91.7
Mean age (SD) Mean (SD)	32.05 (8.06)	34.04 (6.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Relapsing remitting MS No of events	n = 17 ; % = 81	n = 19 ; % = 79.2
Secondary progressive MS No of events	n = 4 ; % = 19	n = 5 ; % = 20.8
EDSS <2	n = 7 ; % = 33.3	n = 6 ; % = 25

Characteristic	Amantadine and aspirin (N = 21)	Amantadine and placebo (N = 24)
No of events		
EDSS 2-5 No of events	n = 4 ; % = 19.1	n = 10 ; % = 41.7
EDSS >5 No of events	n = 10 ; % = 47.6	n = 8 ; % = 33.3
Disease duration (Months) Mean (SD)	43.1 (26.2)	57.8 (43.5)
FSS score Scale range: 1-7. Lower is better. Mean (SD)	5.27 (0.5)	5.36 (0.48)

Outcomes

Study timepoints

- 6 week (This group will be considered as 3-6 months, but will be downgraded for indirectness as the time period is <3 months.)

Combination compared to amantadine alone at 3-6 months - continuous outcomes (final values)

Outcome	Amantadine and aspirin, 6-week, N = 21	Amantadine and placebo, 6-week, N = 24
FSS score Scale range: 1-7. Mean (SD)	3.36 (0.5)	3.96 (0.5)

FSS score - Polarity - Lower values are better

This group will be considered as 3-6 months, but will be downgraded for indirectness as the time period is <3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Combinationcomparedtoamantadinealoneat3-6months-continuousoutcomes(finalvalues)-FSSscore-MeanSD-Amantadine and aspirin-Amantadine and placebo-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to duration of treatment/follow up being less than 3 months)*

Krupp, 1995

Bibliographic Reference	Krupp, L. B.; Coyle, P. K.; Doscher, C.; Miller, A.; Cross, A. H.; Jandorf, L.; Halper, J.; Johnson, B.; Morgante, L.; Grimson, R.; Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo; Neurology; 1995; vol. 45 (no. 11); 1956-1961

Study details

Secondary publication of another included study- see primary study for details	No additional information.

Other publications associated with this study included in review	Geisler, M. W.; Sliwinski, M.; Coyle, P. K.; Masur, D. M.; Doscher, C.; Krupp, L. B.; The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis; Archives of neurology; 1996; vol. 53 (no. 2); 185-188
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	United States of America.
Study setting	Study occurred at three medical centers in the greater metropolitan New York area.
Study dates	No additional information.
Sources of funding	Supported in part by a grant from the National Multiple Sclerosis research foundation #RG2149A1.
Inclusion criteria	People between the ages of 18 and 52 years, were ambulatory, had a Kurtzke EDSS score of 6.0 or less and a baseline FSS score of 4.0 or more.
Exclusion criteria	People with current or recent (within 2 months) use of medications that might influence fatigue (benzodiazepines, antidepressants, azathioprine, or cyclophosphamide); people with severe depression (at least 36 on the Center for Epidemiologic Studies Depression scale).
Recruitment / selection of participants	No additional information.
Intervention(s)	Amantadine 100mg twice a day for 2 months Pemoline for 2 months (this group was extracted as they did not fulfil the inclusion criteria in the protocol). Concomitant therapy: Not stated/unclear.
Comparator	Placebo twice a day for 2 months

Number of participants	93 (27 received pemoline, 31 received amantadine, 35 received placebo).
Duration of follow-up	2 months (8 weeks of treatment, 2 weeks of additional follow up after washout of treatment).
Additional comments	Subgroup information: Type of MS: See participants characteristics table. Majority relapsing-remitting, other population unknown. EDSS: See participants characteristics table. <6. Disease modifying treatment: Not stated/unclear. Dosage: Standard dose. Route of administration: Oral. People receiving palliative care: Not stated/unclear. Continuous outcomes in the Krupp paper were reported as F, p and chi-square scores where it was not possible to extract them into meaningful data for meta-analysis. The Geisler paper uses a subset of participants (participants who had cognitive function tests completed at baseline and follow up) but reports outcomes as means and standard deviations. These outcomes will be used in the analysis.

Study arms

Amantadine (N = 31)

Oral amantadine 100mg twice a day for 2 months

Placebo (N = 35)

Oral placebo twice a day for 2 months

Characteristics

Arm-level characteristics

Characteristic	Amantadine (N = 31)	Placebo (N = 35)
% Female Sample size	n = NR ; % = 68	n = NR ; % = 69
Mean age (SD) Mean (SD)	40.7 (7.1)	41.4 (5.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
% Relapsing-remitting MS Sample size	n = NR ; % = 90	n = NR ; % = 94
Duration of MS from time of symptom onset to study visit (Months) Mean (SD)	136 (167)	80 (68)
EDSS	2.7 (1.8)	2.1 (1.2)

Characteristic	Amantadine (N = 31)	Placebo (N = 35)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 2 month (Will be classified as 3-6 months. However, all outcomes will be downgraded for indirectness due to short follow up period (<3 months).)

Amantadine compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Amantadine, Baseline, N = 31	Amantadine, 2-month, N = 31	Placebo, Baseline, N = 35	Placebo, 2-month, N = 35
Withdrawal due to adverse events Adverse events. Amantadine: Rash and anxiety. Placebo: Excessive sleep disturbance. No of events	n = NA ; % = NA	n = 2 ; % = 6.5	n = NA ; % = NA	n = 1 ; % = 2.9
Sleep disturbance Including the participant who withdrew due to sleep disturbance in the placebo group. No of events	n = NA ; % = NA	n = 2 ; % = 6.5	n = NA ; % = NA	n = 0 ; % = 0
Cardiac disorder/arrhythmia Palpitations	n = NA ; % = NA	n = 1 ; % = 3.2	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Amantadine, Baseline, N = 31	Amantadine, 2-month, N = 31	Placebo, Baseline, N = 35	Placebo, 2-month, N = 35
No of events				

Will be classified as 3-6 months. However, all outcomes will be downgraded for indirectness due to short follow up period (<3 months).

Amantadine compared to placebo at 3-6 months - continuous outcomes (final values)

Outcome	Amantadine, Baseline, N = 16	Amantadine, 2-month, N = 16	Placebo, Baseline, N = 16	Placebo, 2-month, N = 16
Patient-reported outcome measures to assess MS fatigue (FSS) Scale range: 1-7. Mean (SD)	5.5 (1.3)	5.2 (0.8)	5.7 (0.7)	5.4 (1.2)
Long-term retrieval Mean (SD)	37.9 (17.8)	42.2 (17.5)	50.2 (11.6)	45.2 (11.4)
Delayed recall Mean (SD)	8.1 (2.8)	8.9 (3.6)	8.3 (2.9)	8.9 (3.1)
Sum of recall Mean (SD)	48.9 (10.1)	52.3 (10.1)	50.9 (6.9)	53.5 (6.7)
Cognitive functions (Benton Visual Retention) Number of errors Mean (SD)	3.4 (1.1)	4.3 (2.4)	2.6 (1.3)	2.8 (1.8)

Outcome	Amantadine, Baseline, N = 16	Amantadine, 2-month, N = 16	Placebo, Baseline, N = 16	Placebo, 2-month, N = 16
Cognitive functions (WAIS-R Digit Span) Higher indicates better attention Mean (SD)	14.6 (3.3)	15.6 (2.7)	15.9 (2.9)	16.5 (3.5)
Part A Mean (SD)	37.6 (10.9)	30.9 (9.4)	36.8 (15.2)	36.2 (14.2)
Part B Mean (SD)	73.3 (32)	68.9 (31.2)	92.1 (30.1)	83.1 (29.2)
Written Mean (SD)	40.4 (17.9)	48.6 (15.7)	45.1 (10.9)	46.6 (14.2)
Oral Mean (SD)	50.8 (17.5)	57.8 (19.7)	53.4 (13.4)	58.3 (16.8)

Patient-reported outcome measures to assess MS fatigue (FSS) - Polarity - Lower values are better

Cognitive functions (selective reminding) - Polarity - Higher values are better

Cognitive functions (Benton Visual Retention) - Polarity - Lower values are better

Cognitive functions (WAIS-R Digit Span) - Polarity - Higher values are better

Cognitive functions (Trail Making Test) - Polarity - Lower values are better

Cognitive functions (Symbol Digital Modalities Test) - Polarity - Higher values are better

Will be classified as 3-6 months. However, all outcomes will be downgraded for indirectness due to short follow up period (<3 months).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Amantadinecomparedtoplaceboat3-6months-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Amantadine-Placebo-t2

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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-dichotomousoutcomes-Sleepdisturbance-NoOfEvents-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-dichotomousoutcomes-Cardiacdisorder/arrhythmia-NoOfEvents-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(FSS)-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(selectivereminding)-Long-termretrieval-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(selectivereminding)-Delayedrecall-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(selectivereminding)-SumofrecallMeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(BentonVisualRetention)-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(WAIS-RDigitSpan)-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(TrailMakingTest)-PartA-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(TrailMakingTest)-PartB-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(SymbolDigitalModalitiesTest)-Written-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Amantadinecomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Cognitivefunctions(SymbolDigitalModalitiesTest)-Oral-MeanSD-Amantadine-Placebo-t2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Due to short follow up period (<3 months))*

Ledinek, 2013

Bibliographic Reference	Ledinek, Alenka Horvat; Sajko, Mojca Cizek; Rot, Uros; Evaluating the effects of amantadin, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis--result of a pilot randomized, blind study; Clinical neurology and neurosurgery; 2013; vol. 115suppl1; S86-9

Study details

Secondary publication of another included study- see primary study for details	No additional information.

Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study location	Slovenia.
Study setting	Single-centre, outpatient follow up
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	People with a diagnosis of multiple sclerosis according to the McDonald criteria, a stable disability level between 1.0 and 5.5 on the Expanded Disability status Scale and clinical evidence of fatigue documented by modified fatigue impact scale.
Exclusion criteria	Severe depression and hypothyroidism; concomitant drugs use affecting fatigue (including antipsychotic agents, monoamine oxidase inhibitors, benzodiazepines, tricyclic antidepressant drugs, anticonvulsants, beta blockers and barbiturates).
Recruitment / selection of participants	No additional information.
Intervention(s)	1) Amantadine 200mg orally daily for 1 month 2) Modafinil 200mg orally daily for 1 month 3) Acetyl-l-carnitine 2 grams orally daily for 1 month - this group does not fulfil the inclusion criteria for the review and so will not be extracted
Comparator	Placebo daily for 1 month
Number of participants	60 (15 for each intervention)

Duration of follow-up	1 month
Additional comments	Subgroup categories: Type of MS: Not stated/unclear. EDSS: See participant characteristics table. <6. Disease modifying treatment status: Not stated/unclear. Drug doses: Standard doses. Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Amantadine (N = 15)

Amantadine 200mg orally daily for 1 months

Modafinil (N = 15)

Modafinil 200mg orally daily for 1 month

Placebo (N = 15)

Placebo orally daily for 1 month

Characteristics

Arm-level characteristics

Characteristic	Amantadine (N = 15)	Modafinil (N = 15)	Placebo (N = 15)
% Female Sample size	n = 11 ; % = 73.3	n = 8 ; % = 53.3	n = 7 ; % = 46.7
Mean age (SD) Mean (SD)	40.7 (7)	35.6 (2.8)	37.6 (6.3)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
EDSS score Mean (SD)	2.5 (1.1)	2.8 (1)	2.9 (1.1)
Modified fatigue impact scale Score range: 0-84, lower scores are better Mean (SD)	48.3 (20.2)	49 (10.4)	33.8 (12.1)

Outcomes

Study timepoints

- 1 month (This time period will be included in the 3–6-month category, but will be downgraded due to indirectness as the time period is <3 months.)

Amantadine compared to modafinil compared to placebo at 3-6 months - continuous outcomes (final values)

Outcome	Amantadine, 1 month, N = 15	Modafinil, 1 month, N = 15	Placebo, 1 month, N = 15
Patient-reported outcome measures to assess MS fatigue (MFIS score) Score range: 0-84, lower scores are better Mean (95% CI)	31.2 (23.8 to 38.5)	49.4 (42.9 to 56)	48.5 (41.2 to 55.7)
SF-36 physical component summary Mean (95% CI)	34.4 (30.2 to 38.6)	41.5 (37.8 to 45.3)	40.2 (36 to 44.4)
SF-36 mental component summary Mean (95% CI)	48.8 (44.7 to 52.8)	42.8 (39.2 to 46.5)	40.4 (36.3 to 44.4)

Patient-reported outcome measures to assess MS fatigue (MFIS score) - Polarity - Lower values are better

Health-related Quality of Life (SF-36) - Polarity - Higher values are better

This time period will be included in the 3–6-month category, but will be downgraded due to indirectness as the time period is <3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFISscore)-MeanNineFivePercentCI-Amantadine-Modafinil-Placebo-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Health-relatedQualityofLife(SF-36)-SF-36physicalcomponentsummary-MeanNineFivePercentCI-Amantadine-Modafinil-Placebo-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
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 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Health-relatedQualityofLife(SF-36)-SF-36mentalcomponentsummary-MeanNineFivePercentCI-Amantadine-Modafinil-Placebo-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Möller, 2011

Bibliographic Reference	Möller, F.; Poettgen, J.; Broemel, F.; Neuhaus, A.; Daumer, M.; Heesen, C.; HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis; Multiple sclerosis (Houndmills, Basingstoke, England); 2011; vol. 17 (no. 8); 1002-1009

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.

Trial name / registration number	HAGIL study (Hamburg Vigil study).
Study type	Randomised controlled trial (RCT)
Study location	Germany.
Study setting	MS outpatient clinic at University Medical Centre Hamburg-Eppendorf.
Study dates	No additional information.
Sources of funding	Data analysis was partially supported by the Biopharma project 'Neu-Quadrat' funded by the German Ministry of Education and Research. Biopharma Neu2; Plattformprojekte im Neu2-Konsortium; MS-Bildgebung, MS-Klinisches Studienteam und Validierungsstudie, Grant Number: 0315613, German Ministry of Education and Research.
Inclusion criteria	Male and female patients, aged 18 to 65 years, with definite MS according to the McDonald criteria, a score of at least 4 on the Fatigue Severity Scale and an Expanded Disability Status Scale (EDSS) score of <7 were enrolled in the study.
Exclusion criteria	Relapses or steroid courses in the preceding 4 weeks, mitoxantrone treatment or any new medical treatments possibly inducing or worsening fatigue (e.g., interferon) that had been started within the preceding 4 weeks. Symptomatic fatigue treatments had to be discontinued at least 2 weeks before randomisation. Other symptomatic and potentially sedative treatments had to be in a steady-state condition of dosing and effects for at least 4 weeks. Further exclusion criteria were severe neuropsychological deficits (by clinical judgement); severe depression (measured by the mood subscale of the Hamburg Quality of Life Questionnaire in MS; HAQUAMS); and all other psychiatric diagnoses as well as the known contraindications for modafinil, such as ongoing or previous addictive disorders, epilepsy, or simultaneous treatment with alpha-1 antagonists (e.g., prazosin).
Recruitment / selection of participants	No additional information.
Intervention(s)	Modafinil oral 200mg/day up titrated over 1 week, then continued for 8 weeks in total. Concomitant treatment: Not stated/unclear.
Comparator	Placebo daily orally for 8 weeks. Concomitant treatment: Not stated/unclear.

Number of participants	121 randomised (62 modafinil, 59 placebo).
Duration of follow-up	8 weeks.
Additional comments	Subgroup categories: Type of MS: See participant characteristics table. Mixed. EDSS score: See participant characteristics table. <6. Disease modifying treatment status: See participant characteristics table. Mixed. Drug doses: Standard dose. Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Modafinil (N = 62)

200mg/day up titrated over 1 week, then continued for 8 weeks in total

Placebo (N = 59)

Matching placebo for 8 weeks

Characteristics

Study-level characteristics

Characteristic	**Study (N = 121)**
% Female No of events	n = 85 ; % = 70
Mean age (SD) Mean (SD)	41.1 (10.3)
Ethnicity Nominal	NA
Comorbidities Nominal	NA
Relapsing-remitting MS Sample size	n = 63 ; % = 53
Secondary-progressive MS Sample size	n = 31 ; % = 26
Primary-progressive MS Sample size	n = 26 ; % = 21
EDSS score Mean (SD)	3.3 (1.4)

Characteristic	Study (N = 121)
On immunotherapy Sample size	n = 61 ; % = 50.4
Disease duration (years) Mean (SD)	6.9 (5.8)

Arm-level characteristics

Characteristic	Modafinil (N = 62)	Placebo (N = 59)
MFIS Scale range: 0-84. Lower is better. Mean (SD)	54.75 (13.32)	51.2 (11.8)
HAQUAMS Scale range unclear. High is poor. Mean (SD)	12.1 (2.44)	11.86 (2.52)
Epworth Sleepiness scale Scale range: 0-24. Lower is better. Mean (SD)	11.8 (4.89)	11.78 (4.96)

Outcomes

Study timepoints

- 8 week (This group will be included in the 3–6-month category, but will be downgraded due to indirectness as time is <3 months.)

Modafinil compared to placebo at 3-6 months - Continuous outcomes (final values)

Outcome	Modafinil, 8-week, N = 62	Placebo, 8-week, N = 59
Patient-reported outcome measures to assess MS fatigue (MFIS) Scale range: 0-84. Lower is better. Mean (SD)	45.3 (16.3)	44.3 (15.2)
Health-related Quality of Life (HAQUAMS) Scale range unclear Mean (SD)	11.49 (3.29)	11.04 (2.52)
Epworth Sleepiness scale Scale range: 0-24. Mean (SD)	9.69 (4.43)	9.53 (4.94)

Patient-reported outcome measures to assess MS fatigue (MFIS) - Polarity - Lower values are better

Health-related Quality of Life (HAQUAMS) - Polarity - Lower values are better

Epworth Sleepiness scale - Polarity - Lower values are better

This group will be included in the 3–6-month category, but will be downgraded due to indirectness as time is <3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Modafinilcomparedtoplaceboat3-6months-Continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFIS)-MeanSD-Modafinil-Placebo-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period)*

Modafinilcomparedtoplaceboat3-6months-Continuousoutcomes(finalvalues)-Health-relatedQualityofLife(HAQUAMS)-MeanSD-Modafinil-Placebo-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
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 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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period)*

Modafinilcomparedtoplaceboat3-6months-Continuousoutcomes(finalvalues)-EpworthSleepinessscale-MeanSD-Modafinil-Placebo-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 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	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period)*

Murray, 1985

Bibliographic Reference	Murray, T. J.; Amantadine therapy for fatigue in multiple sclerosis; Canadian journal of neurological sciences [Journal canadien des sciences neurologiques]; 1985; vol. 12 (no. 3); 251-254

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.

Study type	Randomised controlled trial (RCT)
Study location	Canada.
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	People with multiple sclerosis and a complaint of fatigue which they felt were abnormal, or greater than normal for more than 3 months and in most the symptom had been present for years.
Exclusion criteria	No additional information.
Recruitment / selection of participants	No additional information.
Intervention(s)	Amantadine 100mg orally twice a day for 3 weeks, then placebo orally twice a day for 3 weeks (1 week washout period between doses)
Comparator	Placebo orally twice a day for 3 weeks, then amantadine 100mg orally twice a day for 3 weeks (1 week washout period between doses)
Number of participants	32
Duration of follow-up	6 weeks
Additional comments	Subgroup categories: Type of MS: Not stated/unclear. EDSS: Most of the participants were in the 0-3 range in the EDSS. Disease modifying treatment status: Not stated/unclear. Drug doses: Standard dose.

	Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Amantadine (N = 32)

Amantadine hydrochloride 100mg orally twice a day

Placebo (N = 32)

Placebo orally twice a day

Characteristics

Study-level characteristics

Characteristic	Study (N = 32)
% Female Nominal	NR
Mean age (SD) Nominal	NR
Ethnicity Nominal	NR

Characteristic	Study (N = 32)
Comorbidities Nominal	NR

Outcomes

Study timepoints

- 6 week (This group will be included in the category for 3-6 months, but will be downgraded for indirectness as time period is <3 months.)

Amantadine compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Amantadine, 6-week, N = 32	Placebo, 6-week, N = 32
Withdrawal due to adverse events Adverse events. Due to nausea and hallucination for the participant on amantadine, and worsening of spasticity for the participant on placebo No of events	n = 1 ; % = 3.1	n = 1 ; % = 3.1

This group will be included in the category for 3-6 months, but will be downgraded for indirectness as time period is <3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Amantadinecomparedtoplaceboat3-6months-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Amantadine-Placebo-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Only some concerns as this is a crossover trial and so the baseline characteristics should be the same as the participants are the same in both groups.)*
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment 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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up period)*

Nourbakhsh, 2021

Bibliographic Reference	Nourbakhsh, Bardia; Revirajan, Nisha; Morris, Bridget; Cordano, Christian; Creasman, Jennifer; Manguinao, Michael; Krysko, Kristen; Rutatangwa, Alice; Auvray, Caroline; Aljarallah, Salman; Jin, Chengshi; Mowry, Ellen; McCulloch, Charles; Waubant,

Emmanuelle; Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial; The Lancet. Neurology; 2021; vol. 20 (no. 1); 38-48

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	Nourbakhsh, Bardia; Revirajan, Nisha; Waubant, Emmanuelle; Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS): Study design for a pragmatic, randomized, double-blind, crossover clinical trial; Contemporary clinical trials; 2018; vol. 64; 67-76
Trial name / registration number	TRIUMPHANT-MS. Clinicaltrials.gov number: NCT03185065.
Study type	Randomised controlled trial (RCT)
Study location	United States of America.
Study setting	Two-center trials (at two academic speciality MS centers). Outpatient follow up.
Study dates	October 4th 2017 to February 27th 2019.
Sources of funding	Research was funded through a Patient-Centered Outcomes Research Institute Award (MS-1511-33689).
Inclusion criteria	18 years of age or older, had a diagnosis of MS (according to the 2010 McDonald criteria), reported fatigue as a symptom, and had a screening Modified Fatigue Impact Scale score >33, had an Expanded Disability Status Scale score at the time of screening 0.0 to 7.0 (inclusive) and were not on any medication for the treatment of fatigue (including the study medications) for at least 2 weeks before the screening visit.
Exclusion criteria	Pregnancy or breastfeeding; having a neurodegenerative disorder other than relapsing and progressive MS; history of coronary artery disease or congestive heart failure; history of untreated hypothyroidism; history of untreated sleep apnoea;

	history of long QT syndrome; history of atrial fibrillation or tachyarrhythmia (other than sinus tachycardia); history of ischaemic or haemorrhagic stroke; history of glaucoma; Tourette syndrome; history of severe untreated anaemia (recent history of blood haemoglobin <9gr/dL); uncontrolled hypertension at screening (history of high blood pressure and screening systolic blood pressure >160 or diastolic blood pressure >100); estimated glomerular filtration rate (GFR) <50 mL/min at screening; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels more than twice the upper limit of normal at screening; terminal medical conditions; ongoing treatment for active malignancy; planned surgery or move within eight months of screening; alcohol or substance abuse in the past year (except marijuana or other cannabinoids); history of intolerance or allergic or anaphylactic reaction to amantadine, modafinil, methylphenidate or any component of the preparation; clinically unstable medical or psychiatric disorders that required acute treatment or as determined by the study PI; concurrent use of monoamine oxidase inhibitors-B; history of hypersensitivity/idiosyncrasy to sympathomimetic amines; inability to communicate or answer questionnaires in English or Spanish.
Recruitment / selection of participants	People were recruited through physicians and clinic referrals, and via advertisement at two academic specialty MS centers (JHU and UCSF MS Clinics).
Intervention(s)	1) Oral amantadine (up to 100mg twice daily) 2) Oral modafinil (up to 100mg twice daily) 3) Oral methylphenidate (up to 10mg twice daily) - This group is not included in the protocol for this review and so will not be extracted and included. Concomitant therapy: Not stated/unclear.
Comparator	Oral placebo twice daily
Number of participants	141.
Duration of follow-up	6 weeks for each treatment with a 2-week washout (30 weeks in total for four treatments and three washout phases)
Additional comments	Subgroup information:

	Type of MS: See participant characteristics table. Mixed. EDSS: See participant characteristics table. <6. Disease modifying treatment: Not stated/unclear. Dose: Standard dose. Route of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Amantadine (N = 141)

Up to 100mg orally twice daily

Modafinil (N = 141)

Up to 100mg orally twice daily

Placebo (N = 141)

Placebo orally twice daily

Characteristics

Study-level characteristics

Characteristic	Study (N = 141)
% Female No of events	n = 109 ; % = 77
Mean age (SD) Mean (SD)	46.8 (10.7)
White No of events	n = 107 ; % = 76
African-American No of events	n = 19 ; % = 13.5
Other No of events	n = 15 ; % = 11
Hispanic No of events	n = 15 ; % = 11
Non-Hispanic No of events	n = 126 ; % = 89
Comorbidities Nominal	NR

Characteristic	Study (N = 141)
Relapsing-remitting MS No of events	n = 106 ; % = 75
Secondary progressive MS No of events	n = 19 ; % = 14
Primary progressive MS No of events	n = 15 ; % = 11
Unknown No of events	n = 1 ; % = 1
EDSS score Median (IQR)	3 (2 to 4.5)
HADS Depression-subscale score Mean (SD)	5.5 (3.3)
MFIS Scale range: 0-84. Lower is better. Mean (SD)	53.9 (11.4)
MFIS physical subscale Scale range: 0-34. Mean (SD)	25.3 (5.9)

Characteristic	Study (N = 141)
MFIS cognitive subscale Scale range: 0-40. Mean (SD)	23.7 (7.2)
MFIS psychosocial subscale Scale range: 0-8. Mean (SD)	4.9 (1.8)
Epworth Sleepiness scale Scale range: 0-34. Lower is better. Mean (SD)	10.5 (5)

Outcomes

Study timepoints

- 6 week (This will be grouped as 3-6 months. However, the outcome will be downgraded due to indirectness as the duration of follow up is <3 months.)

Amantadine compared to modafinil compared to placebo at 3-6 months - continuous outcomes (final values)

Outcome	Amantadine, 6-week, N = 124	Modafinil, 6-week, N = 124	Placebo, 6-week, N = 123
Patient-reported outcome measures to assess MS fatigue (MFIS) Scale range: 0-84. Only the total score is extracted as this was a prespecified outcome, while the individual subscales were posthoc exploratory outcomes.	41.3 (38.8 to 43.7)	39 (36.6 to 41.4)	40.6 (38.2 to 43.1)

Outcome	Amantadine, 6-week, N = 124	Modafinil, 6-week, N = 124	Placebo, 6-week, N = 123
Mean (95% CI)			
Epworth Sleepiness scale Scale range: 0-24. Mean (95% CI)	9.3 (8.6 to 10.1)	8.3 (7.6 to 9.1)	9.4 (8.7 to 10.1)

Patient-reported outcome measures to assess MS fatigue (MFIS) - Polarity - Lower values are better

Epworth Sleepiness scale - Polarity - Lower values are better

This will be grouped as 3-6 months. However, the outcome will be downgraded due to indirectness as the duration of follow up is <3 months.

Amantadine compared to modafinil compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Amantadine, 6-week, N = 127	Modafinil, 6-week, N = 125	Placebo, 6-week, N = 124
Cardiac events/arrhythmias Adverse events. Stated as 'cardiac disorders'. No of events	n = 3 ; % = 2.4	n = 5 ; % = 4	n = 3 ; % = 2.4
Withdrawal due to adverse events Adverse events No of events	n = 3 ; % = 2.4	n = 1 ; % = 0.8	n = 2 ; % = 1.6

This will be grouped as 3-6 months. However, the outcome will be downgraded due to indirectness as the duration of follow up is <3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(MFIS)-MeanNineFivePercentCI-Amantadine-Modafinil-Placebo-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-continuousoutcomes(finalvalues)-EpworthSleepinessscale-MeanNineFivePercentCI-Amantadine-Modafinil-Placebo-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-dichotomousoutcomes-Cardiacevents/arrhythmias-NoOfEvents-Amantadine-Modafinil-Placebo-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Amantadinecomparedtomodafinilcomparedtoplaceboat3-6months-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Amantadine-Modafinil-Placebo-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up duration)*

Nourbakhsh, 2018

Bibliographic Reference	Nourbakhsh, Bardia; Revirajan, Nisha; Waubant, Emmanuelle; Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS): Study design for a pragmatic, randomized, double-blind, crossover clinical trial; Contemporary clinical trials; 2018; vol. 64; 67-76

Study details

Secondary publication of another included study- see primary study for details	Nourbakhsh, Bardia; Revirajan, Nisha; Morris, Bridget; Cordano, Christian; Creasman, Jennifer; Manguinao, Michael; Krysko, Kristen; Rutatangwa, Alice; Auvray, Caroline; Aljarallah, Salman; Jin, Chengshi; Mowry, Ellen; McCulloch, Charles; Waubant, Emmanuelle; Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial; The Lancet. Neurology; 2021; vol. 20 (no. 1); 38-48

Rocca, 2021

Bibliographic Reference	Rocca, M. A.; Valsasina, P.; Colombo, B.; Martinelli, V.; Filippi, M.; Cortico-subcortical functional connectivity modifications in fatigued multiple sclerosis patients treated with fampridine and amantadine; European Journal of Neurology; 2021; vol. 28 (no. 7); 2249-2258

Study details

Trial name / registration number	EudraCT 2010-023678-38.
Study location	Italy
Study dates	Not reported

Sources of funding	Partially supported by grants from the Italian Ministry of Health
Inclusion criteria	Relapsing-remitting MS; EDSS score ≤4.0; and experiencing fatigue (persistent and heavy sense of physical and/or mental tiredness) for at least 6 weeks, as determined during clinical interview.
Exclusion criteria	Not reported.
Recruitment / selection of participants	Screened patents at an institute in Milan, Italy.
Intervention(s)	Amantadine: 100 mg twice daily for 4 weeks. Dose chosen in line with previous clinical trials using amantadine.
Comparator	Placebo: 1 placebo tablet twice daily for 4 weeks.
Number of participants	n=30 randomised to the two groups and analysed (study includes an additional arm of fampridine not relevant to this review protocol).
Duration of follow-up	4 weeks
Additional comments	Subgroup information: Type of MS: relapsing-remitting MS inclusion criterion EDSS score: ≤4.0 inclusion criterion Disease modifying treatment status: majority were taking a disease-modifying treatment (>80%) Drug doses: Standard doses. Routes of administration: Oral. People receiving palliative care: Not stated/unclear. Downgrading for indirectness as time-point <3-month minimum in the protocol

Study arms

Amantadine (N = 15)

Placebo (N = 15)

Characteristics

Arm-level characteristics

Characteristic	**Amantadine (N = 15)**	**Placebo (N = 15)**
% Female Sample size	n = 13 ; % = 86.7	n = 12 ; % = 80
Mean age (SD) Mean (IQR)	41.2 (34-46)	41.9 (33-49)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score	2.5 (2 to 2.5)	2 (1.5 to 2)

Characteristic	Amantadine (N = 15)	Placebo (N = 15)
Median (IQR)		
Disease duration (years) Mean (IQR)	15.5 (9.3-21.0)	12.2 (9-16)
None Sample size	n = 4 ; % = 27	n = 2 ; % = 13
First-line (copaxone or interferon) Sample size	n = 8 ; % = 53	n = 9 ; % = 60
Second-line (fingolimod or natalizumab) Sample size	n = 3 ; % = 20	n = 4 ; % = 27

Outcomes

Study timepoints

- Baseline
- 4 week (4 weeks - end of treatment)

Results - raw data

Outcome	Amantadine, Baseline, N = 15	Amantadine, 4-week, N = 15	Placebo, Baseline, N = 15	Placebo, 4-week, N = 15
Global MFIS score Modified Fatigue Impact Scale. Scale 0-84. Mean (SD)	47.5 (13.3)	39.6 (13.5)	46.3 (16.1)	34.4 (15.1)
Adverse events leading to withdrawal No of events	n = NA ; % = NA	n = 0	n = NA	n = 0 ; % = 0

Global MFIS score - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results_MFIS score_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
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	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(outcome - 4-week time-point <3-month minimum specified in the protocol)*

Results_withdrawal due to adverse events_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 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	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(outcome - 4-week time-point <3-month minimum specified in the protocol)*

Sadeghi-Naini, 2017

Bibliographic Reference	Sadeghi-Naini, M.; Ghazi-zadeh Esslami, G.; Fayyazi, S.; Nabavi, S. M.; Morsali, D.; Ghaffarpour, M.; Low dose aspirin for MS-related fatigue: Results of a pilot, double-blind, randomized trial; Neurology Psychiatry and Brain Research; 2017; vol. 25; 24-30

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.

Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Outpatient follow up.
Study dates	No additional information.
Sources of funding	No additional information.
Inclusion criteria	People with MS and newly subjective fatigue who had not undergone any previous treatments or were under treatment for fatigue but did not respond to it subjectively. Age 18-65 years; EDSS score <6 with subjective report of fatigue.
Exclusion criteria	Presence of other causes for fatigue like depression (Beck Depression index >29); metabolic diseases; cardiovascular and pulmonary diseases; regular use of non-steroidal anti-inflammatory drugs or aspirin during the four weeks prior to the study; history of active peptic ulcer or gastrointestinal bleeding in the six months prior to the study; pregnancy, anaemia and thrombocytopenia documented by screening test done for every patient prior to inclusion in the study; EDSS at least 6; sleep apnoea; narcolepsy; history of alcohol or drug abuse; any patient who had experienced a relapse or had been treated with steroids during the four weeks prior to the study.
Recruitment / selection of participants	People who were diagnosed at the MS Centre of the Department of Neurological Sciences at Mostafa Khomeini Hospital in Tehran were recruited.
Intervention(s)	Oral low dose aspirin (80mg) daily for 8 weeks Concomitant therapy: All people were using the different disease modifying therapies including beta-interferons which were prescribed for them.
Comparator	Oral placebo daily for 8 weeks Concomitant therapy: All people were using the different disease modifying therapies including beta-interferons which were prescribed for them.
Number of participants	120 (56 placebo, 64 aspirin)

Duration of follow-up	8 weeks.
Additional comments	Subgroup categories: Type of MS: Relapsing remitting MS (80), secondary progressive MS (18), primary progressive MS (2). EDSS: See participant characteristics table. Disease modifying therapy: All participants were receiving disease modifying therapy. Dose: Standard dose. Route of administration: Oral. Receiving palliative care: Not stated/unclear.

Study arms

Aspirin (N = 64)

Oral low dose aspirin (80mg) daily for 8 weeks

Placebo (N = 56)

Oral placebo daily for 8 weeks

Characteristics

Study-level characteristics

Characteristic	Study (N = 120)
% Female Nominal	NR
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	Aspirin (N = 64)	Placebo (N = 56)
Mean age (SD) Reports baseline characteristics only for aspirin = 51, placebo = 49. Mean (SD)	32.4 (10.1)	34 (7.8)
EDSS Reports baseline characteristics only for aspirin = 51, placebo = 49. Mean (SD)	2 (0.98)	1.5 (1.3)
Disease duration (month) Reports baseline characteristics only for aspirin = 51, placebo = 49. Mean (SD)	81.5 (74.2)	76.4 (58)

Characteristic	Aspirin (N = 64)	Placebo (N = 56)
Depression (Beck Depression Inventory-2) Reports baseline characteristics only for aspirin = 51, placebo = 49. Mean (SD)	18.4 (10.8)	18 (10.8)
MFIS Scale range: 0-84. Lower is better. Reports baseline characteristics only for aspirin = 51, placebo = 49. Mean (SD)	42.7 (17.5)	38.5 (17.8)

Outcomes

Study timepoints

- 8 week (Any outcomes will be grouped as 3-6 months. However, outcomes will be downgraded for indirectness due to short follow up period.)

Aspirin compared to placebo at 3-6 months - dichotomous outcomes

Outcome	Aspirin, 8-week, N = 64	Placebo, 8-week, N = 56
Withdrawal due to adverse events Aspirin: 2 due to GI complaints, 1 due to dizziness and headache. Placebo: 2 due to GI complaints, 1 due to eczema, 2 nonspecific). No of events	n = 5 ; % = 7.8	n = 3 ; % = 5.4

Any outcomes will be grouped as 3-6 months. However, outcomes will be downgraded for indirectness due to short follow up period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Aspirincomparedtoplaceboat3-6months-dichotomousoutcomes-Withdrawalduetoadverseevents-NoOfEvents-Aspirin-Placebo-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Due to short follow up time)*

Shaygannejad, 2012

Bibliographic Reference	Shaygannejad, V.; Janghorbani, M.; Ashtari, F.; Zakeri, H.; Comparison of the effect of aspirin and amantadine for the treatment of fatigue in multiple sclerosis: a randomized, blinded, crossover study; Neurological research; 2012; vol. 34 (no. 9); 854-858

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Iran.
Study setting	Outpatient follow up at the neurology clinics of Isfahan University of Medical Sciences, Iran.
Study dates	October 2009 to September 2010.
Sources of funding	No additional information.
Inclusion criteria	Men and women 13 to 55 years of age with a clinical or laboratory supported diagnosis of multiple sclerosis; an EDSS score of no more than 6 and clinical evidence of fatigue as documented by a score of at least 4 on the Fatigue Severity Score, but no clinical MS exacerbations for at least 4 weeks. None of the people had been treated with medication known to influence MS-related fatigue. People had received interferon-beta treatment for at least 1 year in order to avoid the frequent occurrence of fatigue in the early stage of interferon-beta therapy.
Exclusion criteria	The use of aspirin, non-steroidal anti-inflammatory drugs or MS fatigue medications within the previous 8 weeks; aspirin or NSAID allergy; asthma; peptic ulcer disease or gastrointestinal bleeding; anaemia; thrombocytopenia; bleeding diathesis; hepatic or renal disease; hypothyroidism; recent major illness; untreated depression; narcolepsy; sleep apnoea; history of alcohol or drug abuse; history of uncontrolled seizure or suicidal ideation; or an episode of severe depression within the 3 months before enrolment; lactation and pregnancy as determined by history, physical examination and screening blood tests; women of childbearing potential who were not using a clinically accepted method of contraception.

Recruitment / selection of participants	Consecutive patients.
Intervention(s)	Oral amantadine 100mg twice daily for 4 weeks Concomitant therapy: All people had received interferon-beta treatment for the past year.
Comparator	Oral aspirin 500mg once daily for 4 weeks Concomitant therapy: All people had received interferon-beta treatment for the past year.
Number of participants	52 (26 in each group)
Duration of follow-up	10 weeks (4 weeks for each treatment and a 2-week washout period)
Additional comments	Subgroup information: Type of MS: See participant characteristics table. Mixed. EDSS: See participant characteristics table. <6. Disease modifying treatment: All participants were receiving disease modifying treatment. Dose: Standard doses. Route of administration: Oral. Receiving palliative care: Not stated/unclear.

Study arms

Amantadine (N = 26)

Oral amantadine 100mg twice daily for 4 weeks

Aspirin (N = 26)

Oral aspirin 500mg once daily for 4 weeks

Characteristics

Arm-level characteristics

Characteristic	Amantadine (N = 26)	Aspirin (N = 26)
% Female No of events	n = 22 ; % = 84.6	n = 20 ; % = 78.9
Mean age (SD) Mean (SD)	35.6 (7.8)	35 (7.8)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Avonex	n = 8 ; % = 30.8	n = 18 ; % = 69.2

Characteristic	Amantadine (N = 26)	Aspirin (N = 26)
No of events		
Rebif No of events	n = 9 ; % = 34.6	n = 7 ; % = 26.9
Betaferon No of events	n = 9 ; % = 34.6	n = 1 ; % = 3.8
EDSS Mean (SD)	1.5 (1.8)	1.7 (1.4)
Duration of MS (years) Mean (SD)	3 (1.7)	3 (1.9)
Fatigue Severity Scale Scale range: 1-7. Lower is better. Mean (SD)	4.8 (1.4)	4.6 (1.4)
Relapsing-remitting Sample size	n = 22 ; % = 84.6	n = 22 ; % = 84.6
Secondary progression Sample size	n = 4 ; % = 15.4	n = 4 ; % = 15.4

Outcomes

Study timepoints

- 10 week (The outcomes reported will be grouped in 3-6 months. However, any outcome will be downgraded for indirectness due to short follow up period.)

Admantadine compared to aspirin at 3-6 months - continuous outcomes (final value)

Outcome	Amantadine, 10-week, N = 26	Aspirin, 10-week, N = 26
Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) Scale range: 1-7. Values are the combination of first round and second round means and standard deviations. Mean (SD)	3.75 (1.52)	3.55 (1.55)

Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) - Polarity - Lower values are better

The outcomes reported will be grouped in 3-6 months. However, any outcome will be downgraded for indirectness due to short follow up period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Admantadinecomparedtoaspirinat3-6months-continuousoutcomes(finalvalue)-Patient-reportedoutcomemeasurestoassessMSfatigue(FatigueSeverityScale)-MeanSD-Amantadine-Aspirin-t10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Some concerns
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	Partially applicable *(Due to short follow up period)*

Stankoff, 2005

Bibliographic Reference	Stankoff, B.; Waubant, E.; Confavreux, C.; Edan, G.; Debouverie, M.; Rumbach, L.; Moreau, T.; Pelletier, J.; Lubetzki, C.; Clanet, M.; Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study; Neurology; 2005; vol. 64 (no. 7); 1139-1143

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	Conducted by the members of the French Modafinil Study Group.
Study type	Randomised controlled trial (RCT)
Study location	France.
Study setting	Outpatient follow up.
Study dates	May 2001 and December 2001.
Sources of funding	Supported by Cephalon.
Inclusion criteria	Men and women, 18 to 65 years of age, with MS according to the Poser criteria and complaining of fatigue. Subjects had relapsing remitting or progressive MS, chronic fatigue for at least 6 months with a global score at the Modified Fatigue Impact Scale (MFIS) ≥45, and an Expanded Disability Status Scale score between 0 and 6.5 inclusive.
Exclusion criteria	Relapse or steroid course in the 2 months before randomisation; pregnancy or breastfeeding; uncontrolled depressive disorder (attested by the Montgomery/Asberg Depression Rating Scale [MADRS] score at least 20), anxiety (attested by the Covi Anxiety Scale [CAS] score at least 3) and dementia.
Recruitment / selection of participants	No additional information.

Intervention(s)	Oral modafinil 200mg for 1 week, increased by 100mg every week up to 400mg/day and remaining at that dose between day 31 and day 35 (5 weeks treatment in total). Concomitant treatment: Disease-modifying therapies such as beta interferon, glatiramer acetate, azathioprine or methotrexate were allowed, but had to be t a stable dose for at least 6 months before treatment. All symptomatic treatment for fatigue had to be withdrawn at least 14 days before randomisation.
Comparator	Oral placebo for 5 weeks. Concomitant treatment: Disease-modifying therapies such as beta interferon, glatiramer acetate, azathioprine or methotrexate were allowed, but had to be t a stable dose for at least 6 months before treatment. All symptomatic treatment for fatigue had to be withdrawn at least 14 days before randomisation.
Number of participants	115 (59 modafinil, 56 placebo).
Duration of follow-up	5 weeks.
Additional comments	Subgroup categories: Type of MS: Relapsing-remitting or progressive MS EDSS: See participants characteristics table. <6. Disease modifying treatment status: Unclear. People were allowed to continue previous treatment. Drug doses: Standard dose. Routes of administration: Oral. People receiving palliative care: Not stated/unclear.

Study arms

Modafinil (N = 59)

Oral modafinil 200mg for 1 week, increased by 100mg every week up to 400mg/day and remaining at that dose between day 31 and day 35 (5 weeks treatment in total).

Placebo (N = 56)

Oral placebo for 5 weeks

Characteristics

Arm-level characteristics

Characteristic	Modafinil (N = 59)	Placebo (N = 56)
% Female Sample size	n = NR ; % = 61	n = NR ; % = 75
Mean age (SD) Mean (SD)	43.8 (8)	44 (9)
Ethnicity Nominal	NR	NR
Comorbidities	NR	NR

Characteristic	Modafinil (N = 59)	Placebo (N = 56)
Nominal		
EDSS score Mean (SD)	3.3 (1.8)	3.6 (1.6)
MFIS global score Mean (SD)	63.1 (9.3)	63.3 (10)

Outcomes

Study timepoints

- 5 week (This group will be included in 3-6 months. However, all outcomes will be downgraded for indirectness due to the duration of follow up being <3 months.)

Modafinil compared to placebo at 3-6 months (continuous outcomes - final values)

Outcome	Modafinil, 5-week, N = 59	Placebo, 5-week, N = 56
Patient-reported outcome measures to assess MS fatigue (global MFIS score) Scale range: 0-84. Mean (SD)	52.3 (18.5)	49.2 (16.6)

Patient-reported outcome measures to assess MS fatigue (global MFIS score) - Polarity - Lower values are better

This group will be included in 3-6 months. However, all outcomes will be downgraded for indirectness due to the duration of follow up being <3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

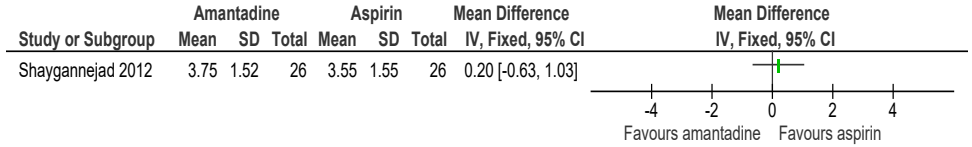
Modafinilcomparedtoplaceboat3-6months(continuousoutcomes-finalvalues)-Patient-reportedoutcomemeasurestoassessMSfatigue(globalMFISscore)-MeanSD-Modafinil-Placebo-t5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
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 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
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	Partially applicable *(Downgraded due to short follow up period (<3 months))*

Appendix E – Forest plots

Amantadine compared to aspirin

Figure 2: Patient-reported outcome measures to assess MS fatigue (FSS, 1-7, lower values are better, final value, crossover trial) at 3-6 months



Amantadine compared to modafinil

Figure 3: Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value, parallel trial and crossover trial) at 3-6 months

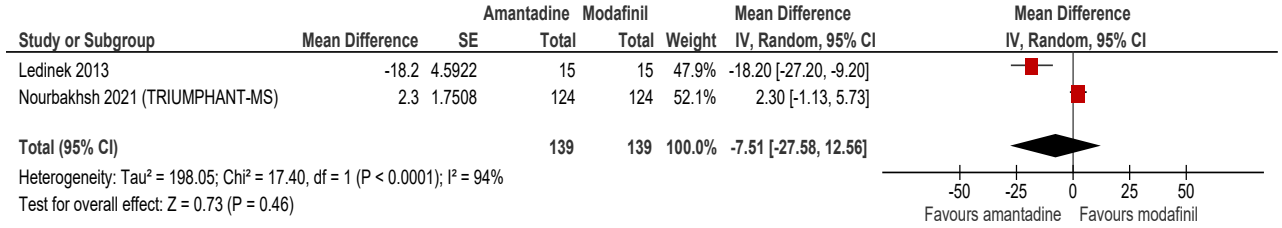


Figure 4: Withdrawal due to adverse events at 3-6 months (crossover)

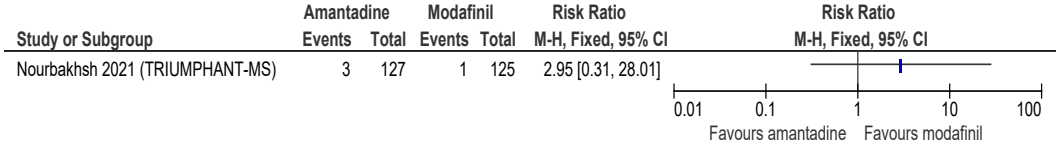


Figure 5: Cardiac events/arrhythmias at 3-6 months (crossover)

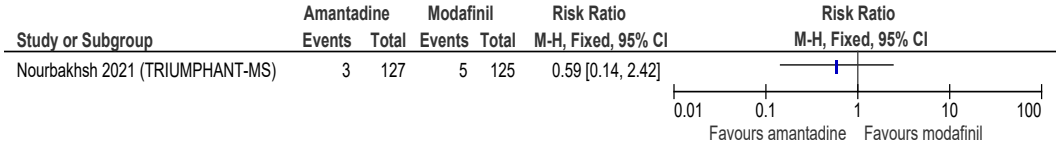


Figure 6: Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

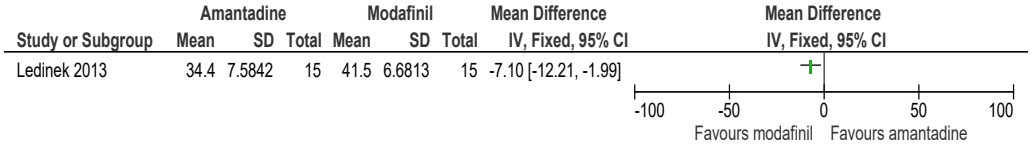


Figure 7: Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

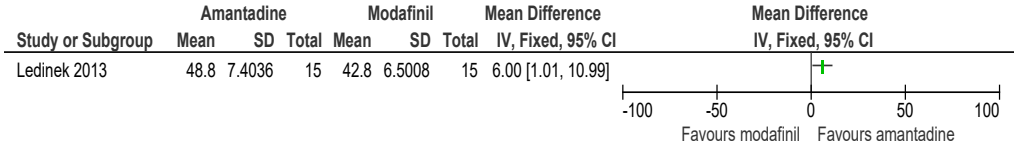
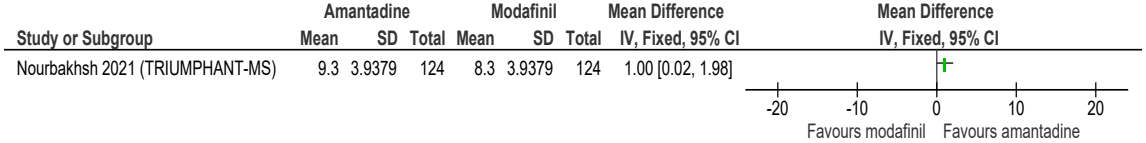
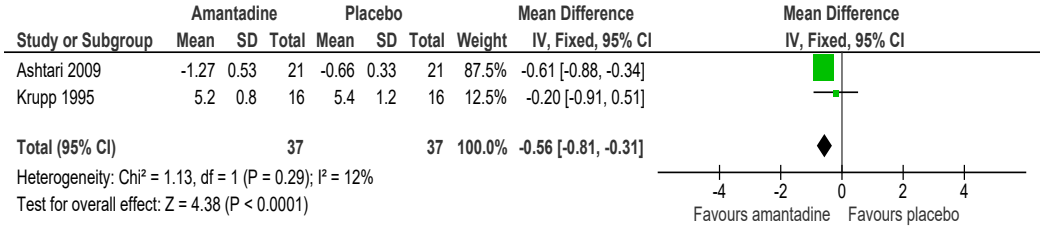


Figure 8: Epworth Sleepiness scale (0-24, lower values are better, final value, crossover trial) at 3-6 months



Amantadine compared to placebo

Figure 9: Patient-reported outcome measures to assess MS fatigue (FSS, 1-7, lower values are better, change score and final value, parallel trials) at 3-6 months



Ashtari 2009 had differences in baseline values (amantadine: 5.27 [1.11], placebo: 4.89 [1.13]).

Figure 10: Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value, parallel trial and crossover trial) at 3-6 months

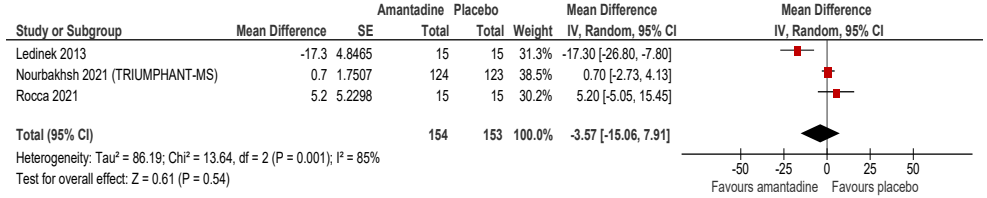


Figure 11: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - energy level, 1-5, higher values are better, final values, crossover trial) at 3-6 months

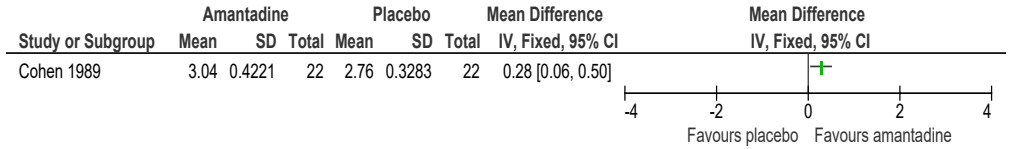


Figure 12: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - muscle strength, 1-5, higher values are better, final values, crossover trial) at 3-6 months

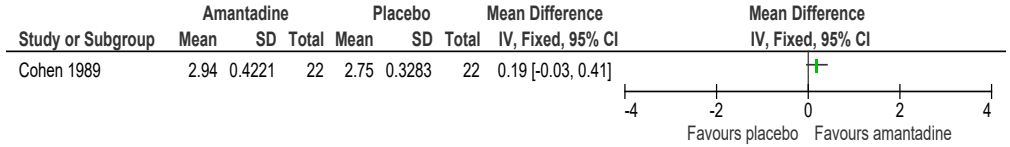


Figure 13: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - concentration/memory, 1-5, higher values are better, final values, crossover trial) at 3-6 months

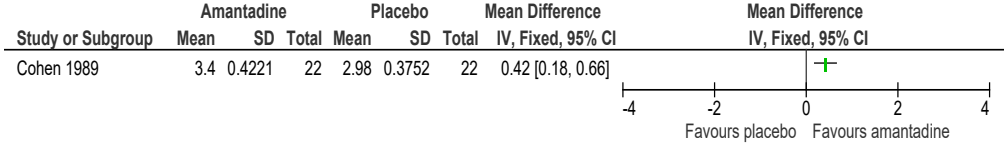


Figure 14: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - motivation level, 1-5, higher values are better, final values, crossover trial) at 3-6 months

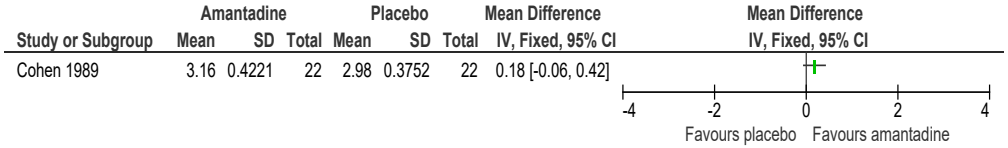


Figure 15: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - ability to finish task, 1-5, higher values are better, final values, crossover trial) at 3-6 months

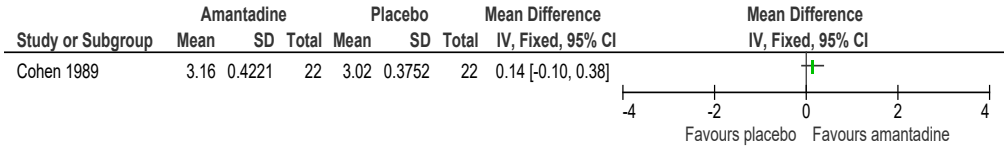


Figure 16: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - ability to solve problem, 1-5, higher values are better, final values, crossover trial) at 3-6 months

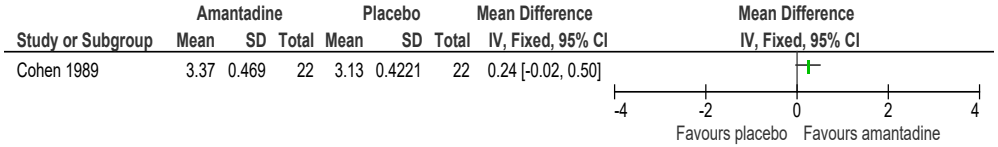


Figure 17: Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - wellbeing, 1-5, higher values are better, final values, crossover trial) at 3-6 months

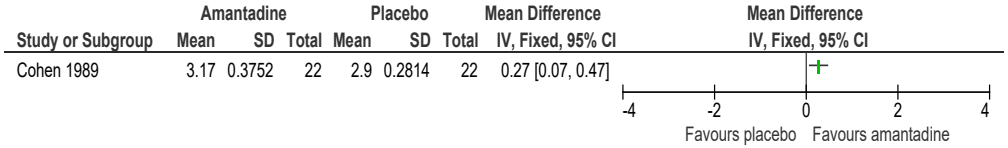


Figure 18: Adverse events leading to withdrawal at 3-6 months (parallel trial and crossover trials)

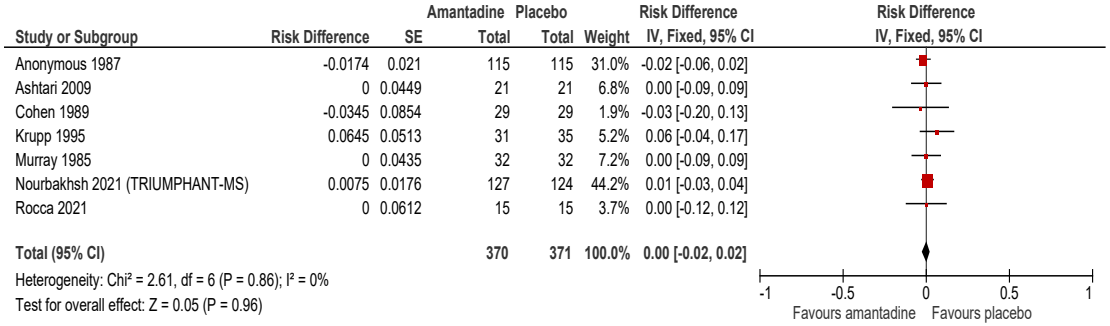


Figure 19: Disruption of sleep at 3-6 months (parallel trial and crossover trial)

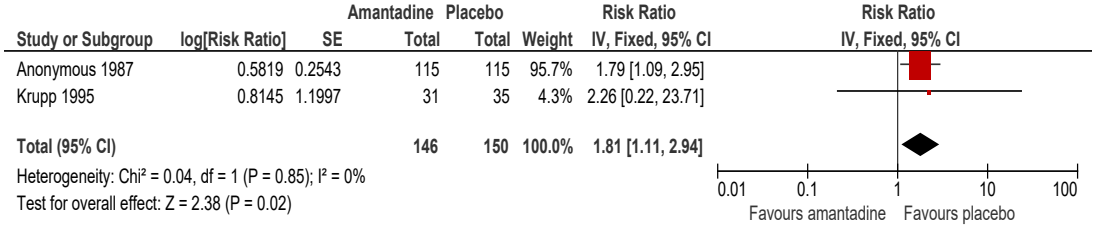


Figure 20: Cardiac events/arrhythmias at 3-6 months (parallel trial and crossover trials)

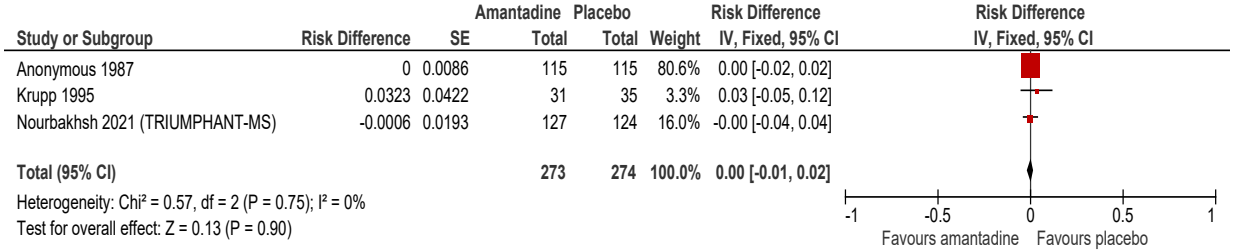


Figure 21: Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

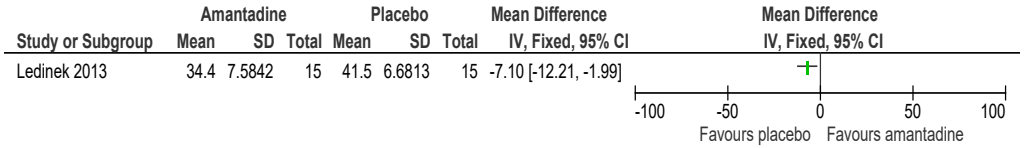


Figure 22: Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

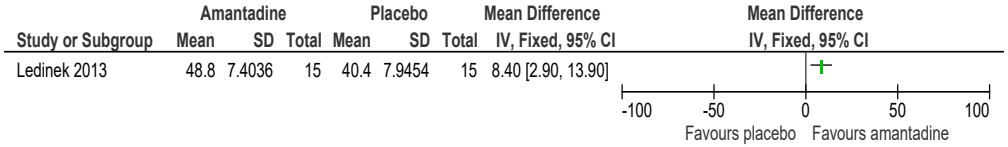


Figure 23: Cognitive functions (13-item activities of daily living intellectual function factor, 0-50, lower values are better, final value, crossover trial) at 3-6 months

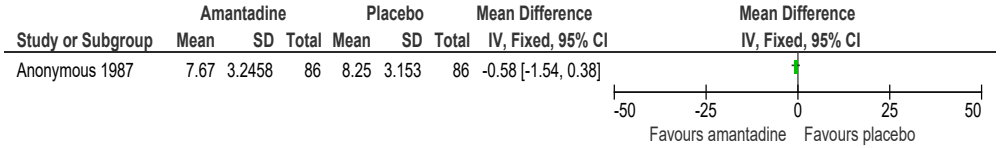
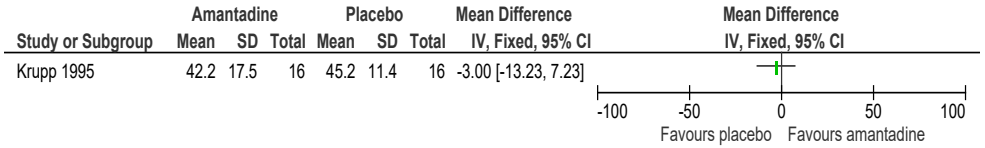


Figure 24: Cognitive functions (selective reminding - long-term retrieval, higher values are better, final value) at 3-6 months



Different baseline values for outcome (amantadine: 37.9 [17.8], placebo: 50.2 [11.6]).

Figure 25: Cognitive functions (selective reminding - delayed recall, higher values are better, final value) at 3-6 months

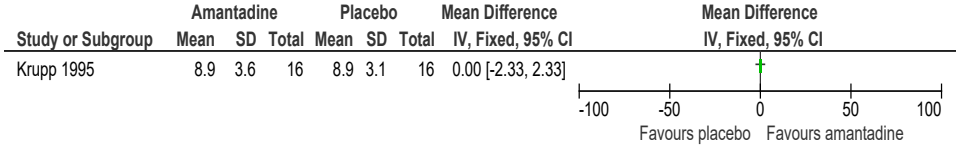


Figure 26: Cognitive functions (selective reminding - sum of recall, higher values are better, final value) at 3-6 months

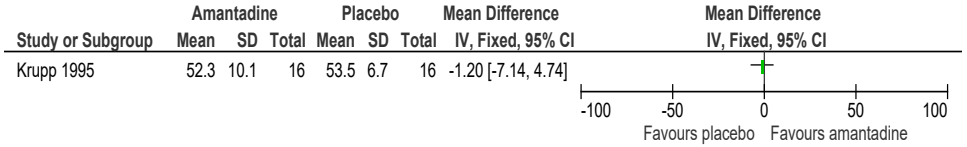


Figure 27: Cognitive functions (Benton Visual Retention, lower values are better, final value) at 3-6 months

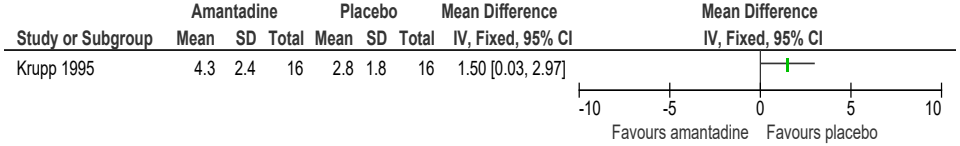


Figure 28: Cognitive functions (WAIS-R Digit Span, higher values are better, final value) at 3-6 months

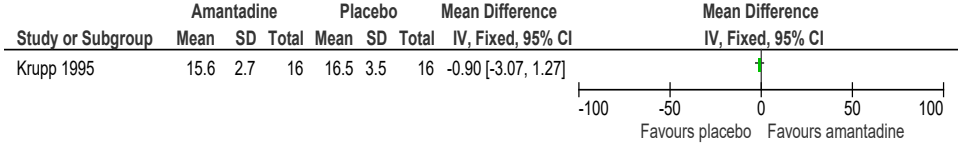


Figure 29: Cognitive functions (Trail Making Test - Part A, lower values are better, final value) at 3-6 months

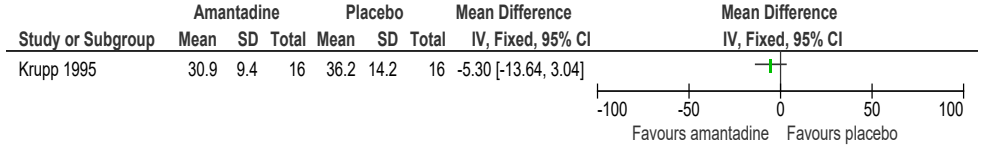
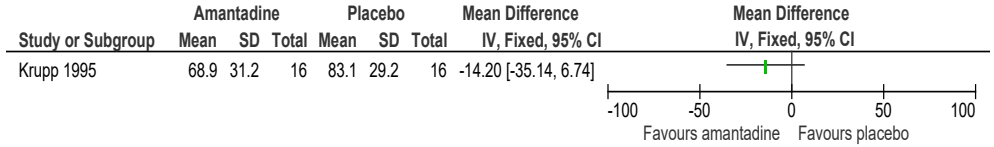


Figure 30: Cognitive functions (Trail Making Test - Part B, lower values are better, final value) at 3-6 months



Different baseline values for outcome (amantadine: 73.3 [32], placebo: 92.1 [30.1]).

Figure 31: Cognitive functions (symbol digit modalities test - written, higher values are better, final value) at 3-6 months

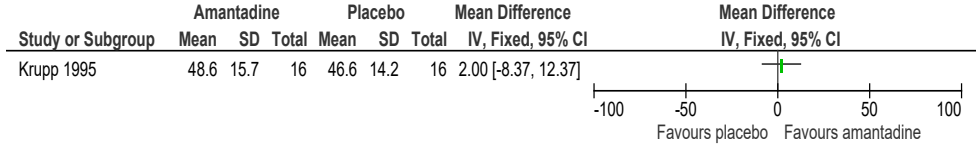


Figure 32: Cognitive functions (symbol digit modalities test - oral, higher values are better, final value) at 3-6 months

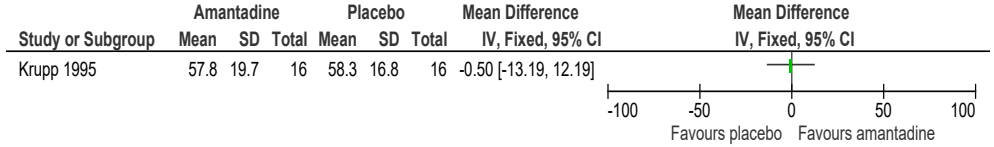


Figure 33: Psychological symptoms (Beck Depression Inventory, 0-63, lower values are better, final value, crossover trial) at 3-6 months

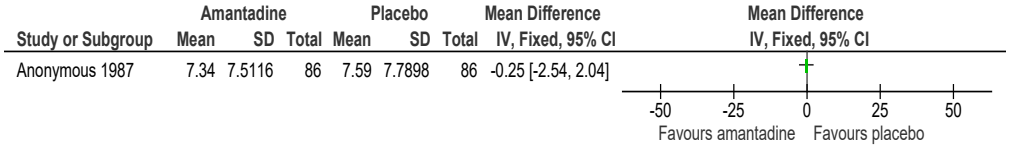
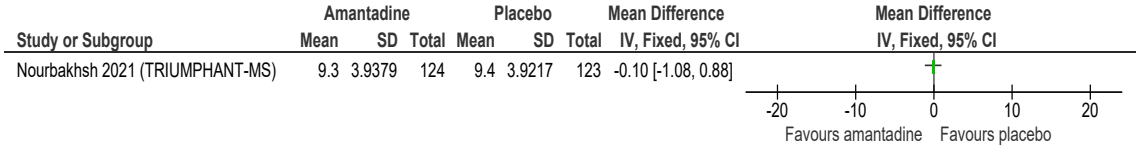


Figure 34: Epworth Sleepiness scale (0-24, lower values are better, final value, crossover trial) at 3-6 months



SSRIs compared to placebo

Figure 35: Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value) at 3-6 months

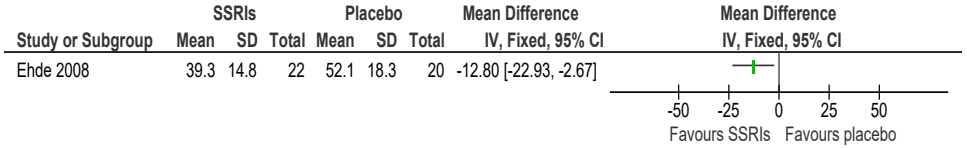


Figure 36: Patient-reported outcome measures to assess MS fatigue (Modified fatigue impact scale, Neurological Fatigue Index Summary Score [different scale ranges], lower values are better, final values, parallel trials) at >6 months-1 year

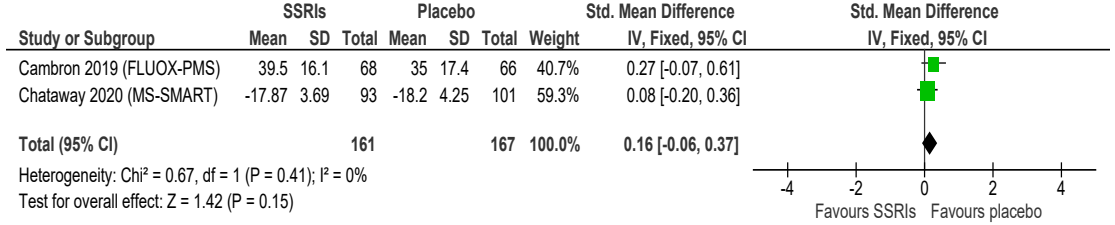


Figure 37: Adverse events leading to withdrawal at >6 months-1 year (parallel trial)

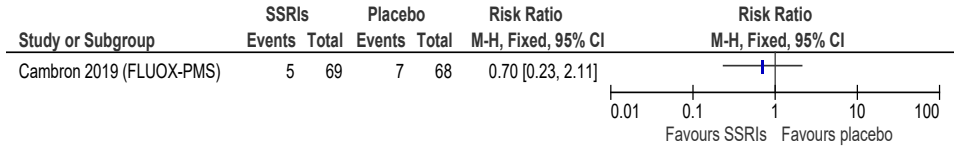


Figure 38: Disruption to sleep at >6 months-1 year (parallel trial)

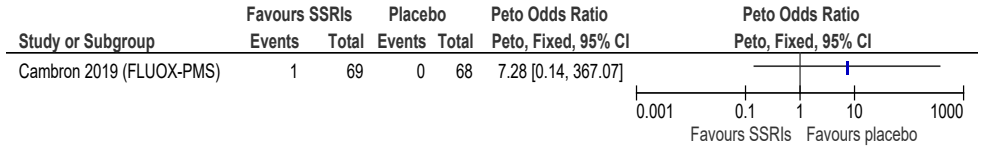


Figure 39: Cardiac events/arrhythmias at >6 months-1 year (parallel trial)

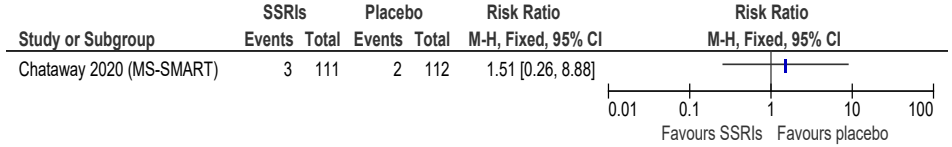


Figure 40: Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

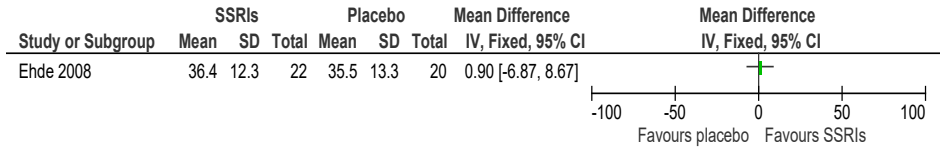


Figure 41: Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

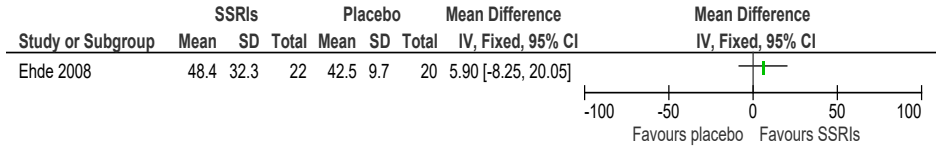


Figure 42: Health-related Quality of Life (EQ-5D-5L utility index score, -0.11-1, higher values are better, final value, parallel trial) at >6 months-1 year

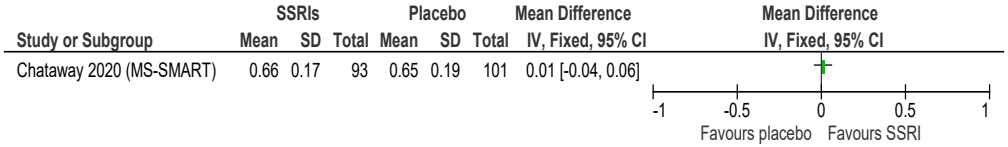


Figure 43: Health-related Quality of Life (EQ-5D-5L visual analogue scale score, 0-100, higher values are better, final value, parallel trial) at >6 months-1 year

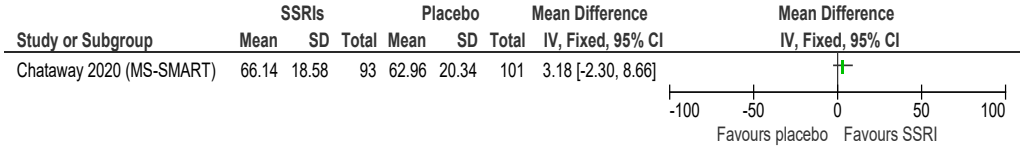


Figure 44: Cognitive functions (PDQ, 0-100, lower values are better, final value, parallel trial) at 3-6 months

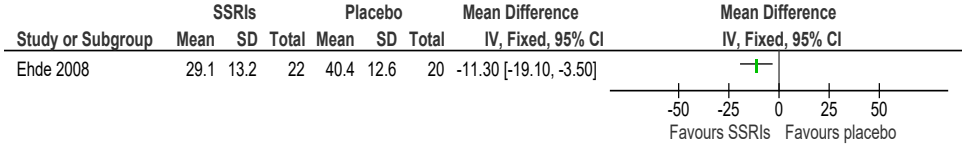


Figure 45: Cognitive functions (Symbol digit modalities test, higher values are better, final value, parallel trials) at >6 months-1 year

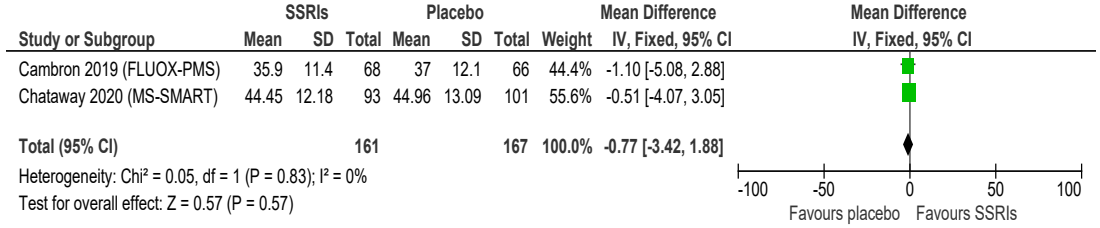


Figure 46: Cognitive functions (California verbal learning test-II, higher values are better, final value, parallel trial) at >6 months-1 year

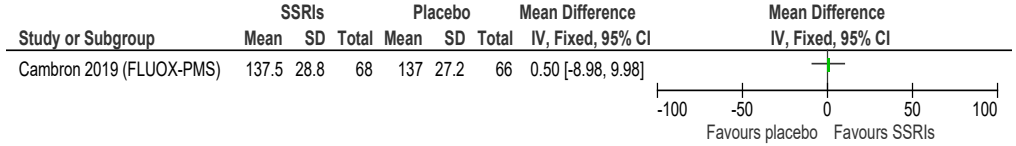


Figure 47: Cognitive functions (Controlled oral word association test - semantic, higher values are better, final value, parallel trial) at >6 months-1 year

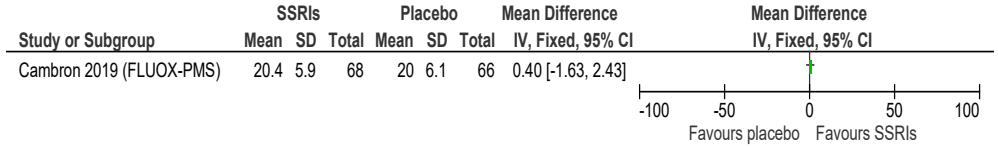


Figure 48: Cognitive functions (Controlled oral word association test - phonetic, higher values are better, final value, parallel trial) at >6 months-1 year

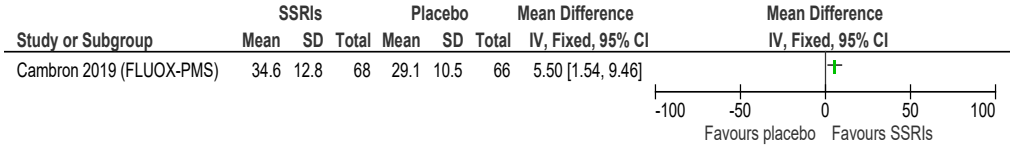


Figure 49: Psychological symptoms (HAM-D, 0-50, lower values are better, final value, parallel trial) at 3-6 months

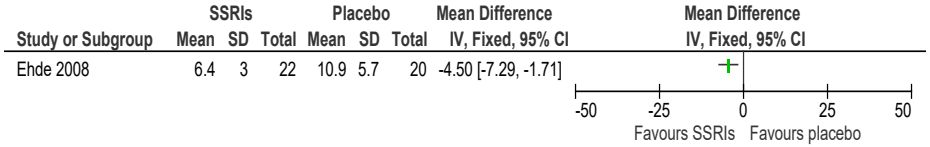
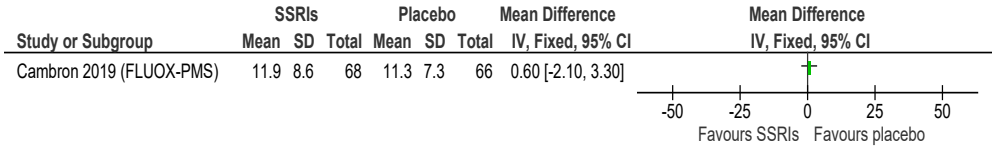


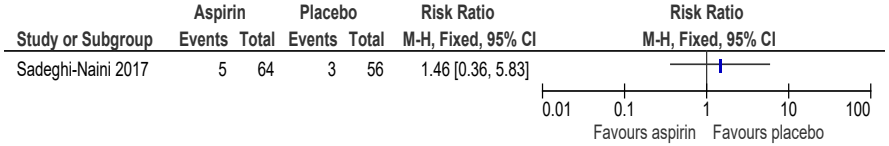
Figure 50: Psychological symptoms (Beck depression inventory-II, 0-63, lower values are better, final values, parallel trial) at >6 months-1 year



Different baseline values for the outcome (SSRIs: 14.7 [10.07], Placebo: 11.3 [6.43]).

Aspirin compared to placebo

Figure 51: Withdrawal due to adverse events at 3-6 months (parallel trial)



Modafinil compared to placebo

Figure 52: Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale Total Score, 0-84, lower values are better, final value, parallel trial and crossover trials) at 3-6 months

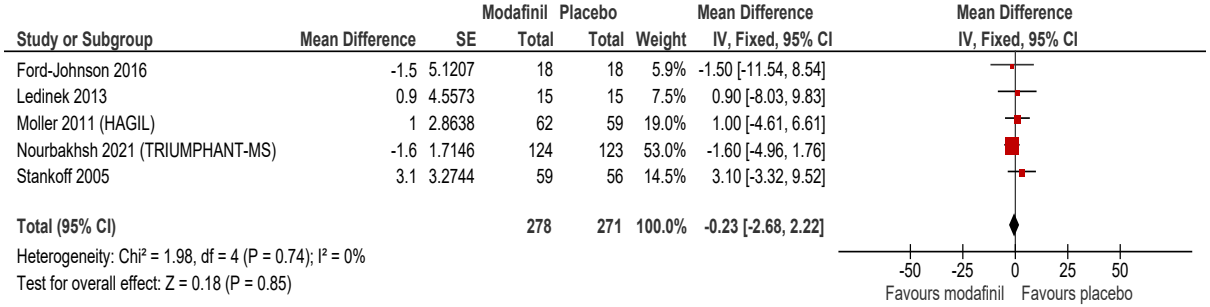


Figure 53: Withdrawal due to adverse events (crossover trials) at 3-6 months

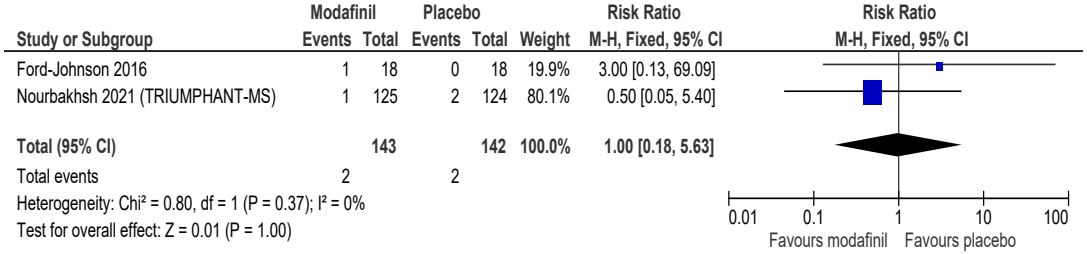


Figure 54: Cardiac events/arrhythmias at 3-6 months (crossover trial)

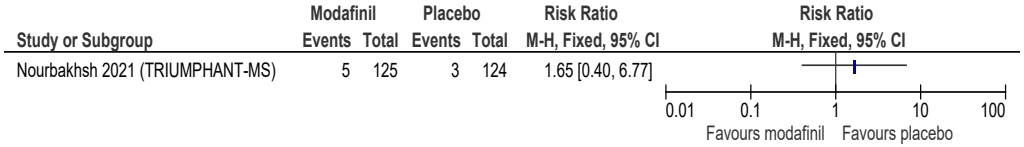


Figure 55: Health-related Quality of Life (HAQUAMS, scale range unclear, lower values are better, final value, parallel trial) at 3-6 months

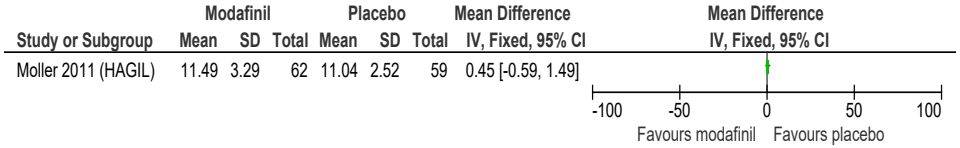


Figure 56: Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

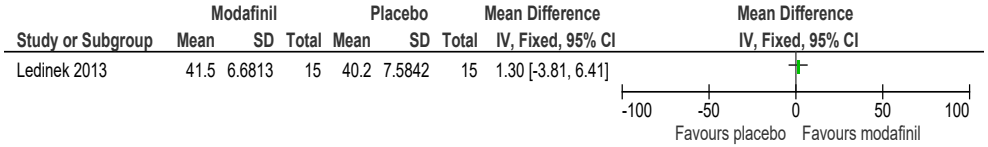


Figure 57: Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months

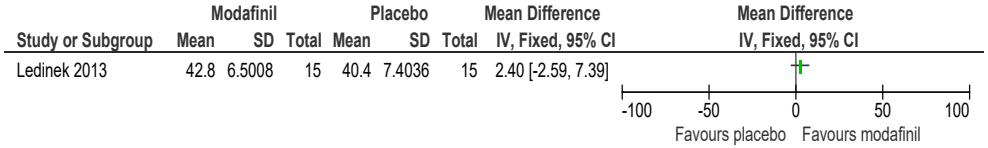


Figure 58: Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Bodily pain, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months

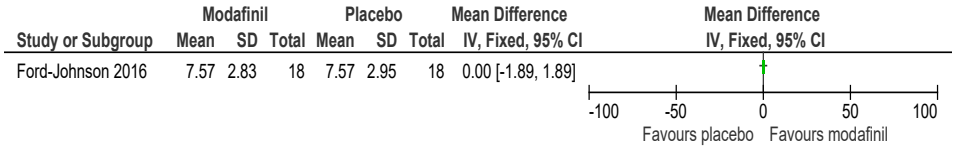
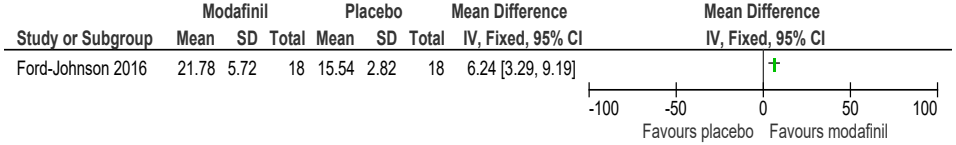
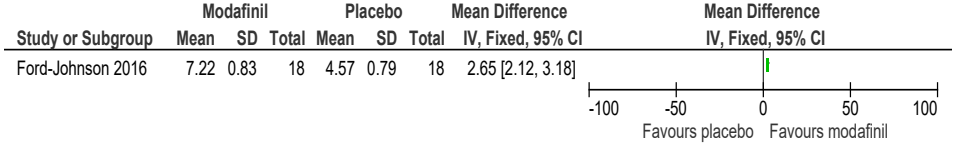


Figure 59: Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Physical functioning, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months



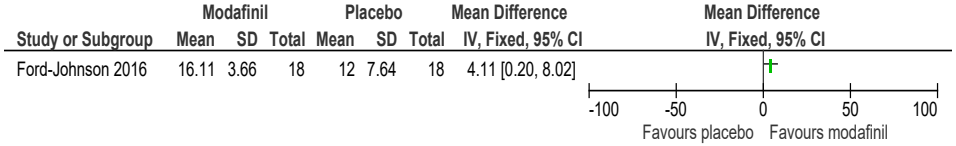
Different baseline values for outcome (modafinil: 21.78 [5.72], placebo: 15.43 [3.82]).

Figure 60: Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - role physical, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months



Different baseline values for outcome (modafinil: 7.22 [0.83], placebo: 4.57 [0.79]).

Figure 61: Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - vitality scale, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months



Different baseline values for outcome (modafinil: 16.11 [3.66], placebo: 12 [7.64]).

Figure 62: Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - General health, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months

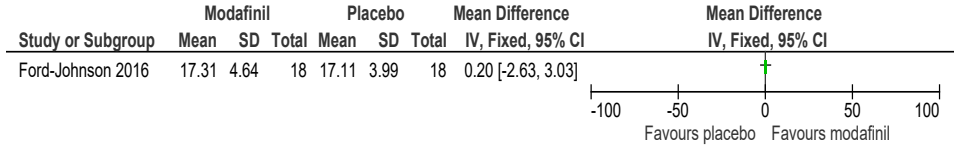


Figure 63: Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Mental health, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months

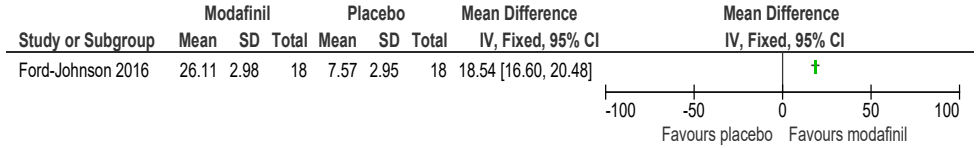
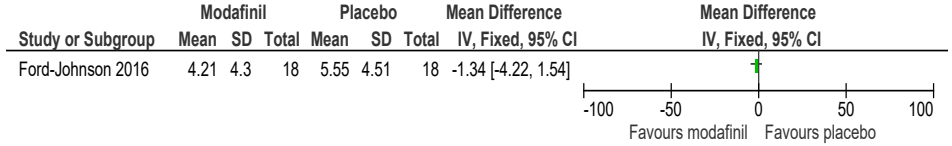
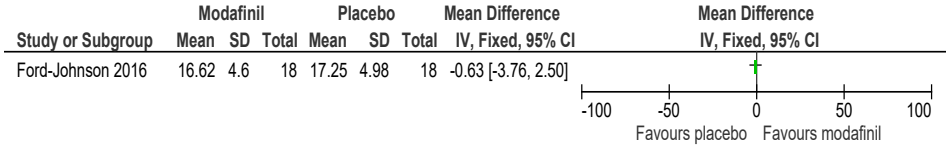


Figure 64: Cognitive functions (Digit Vigilance Test total errors, lower values are better, final value, crossover trial) at 3-6 months



Different baseline values for outcome (modafinil: 2.5 [2.27], placebo: 4.6 [1.82]).

Figure 65: Cognitive functions (Weschler Adult Intelligence Scale-III Digit Span Total, higher values are better, final value, crossover trial) at 3-6 months



Different baseline values for outcome (modafinil: 17.11 [6.23], placebo: 15.63 [1.92]).

Figure 66: Cognitive functions (Weschler Adult Intelligence Scale-III Letter Number Sequencing, higher values are better, final value, crossover trial) at 3-6 months

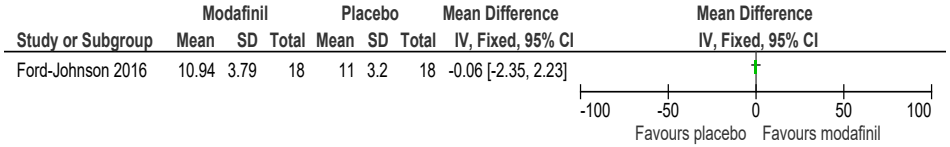
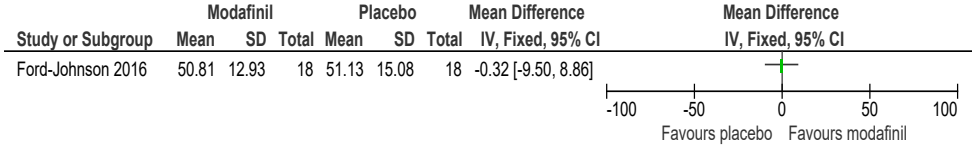
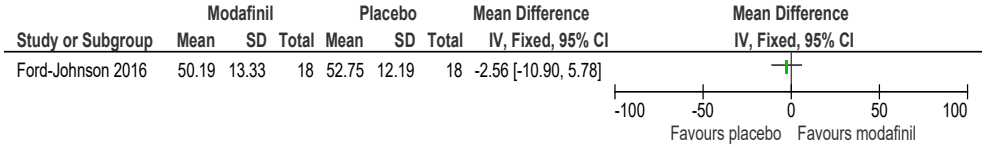


Figure 67: Cognitive functions (symbol digit modalities test, higher values are better, final value, crossover trial) at 3-6 months



Different baseline values for outcome (modafinil: 52.78 [13.09], placebo: 40.25 [12.17]).

Figure 68: Cognitive functions (California Verbal Learning Test - Second Edition, higher values are better, final value, crossover trial) at 3-6 months



Different baseline values for outcome (modafinil: 52.44 [8.96], placebo: 48.63 [9.96]).

Figure 69: Psychological symptoms (The State Trait Anxiety Inventory, 0-60, lower values are better, final value, crossover trial) at 3-6 months

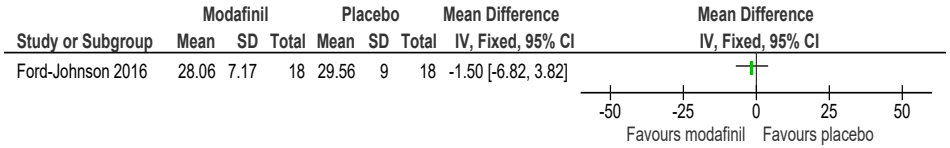


Figure 70: Psychological symptoms (Chicago Multiscale Depression Inventory Total Score, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months

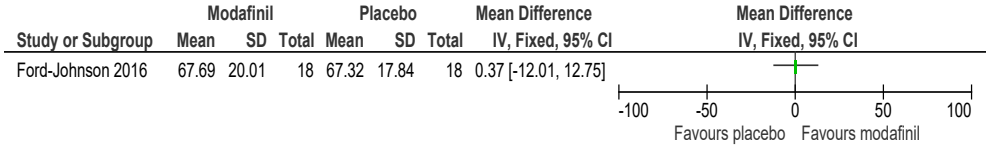
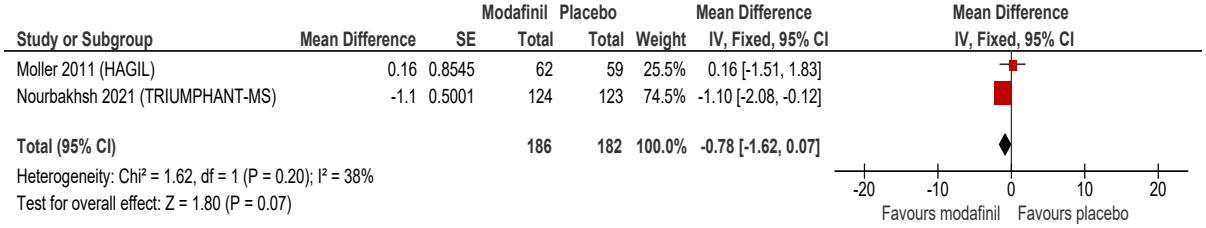
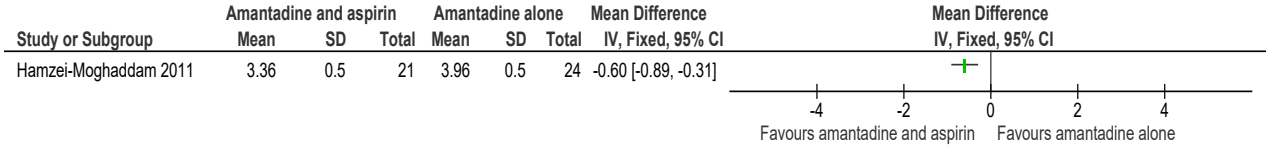


Figure 71: Epworth Sleepiness scale (0-24, lower values are better, final values, parallel trial and crossover trial) at 3-6 months



Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

Figure 72: Patient-reported outcome measures to assess MS fatigue (FSS score, 1-7, lower values are better, final values, parallel trial) at 3-6 months



Appendix F – GRADE and/or GRADE-CERQual tables

Amantadine compared to aspirin

Table 19: Clinical evidence profile: amantadine compared to aspirin for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	aspirin	Relative (95% CI)	Absolute (95% CI)		
Patient-reported outcome measures to assess MS fatigue (FSS, 1-7, lower values are better, final value, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: FSS; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	26	26	-	MD **0.2 higher** (0.63 lower to 1.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of outcome indirectness

c. MID = 0.7 (0.5 x median baseline SD)

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 Amantadine compared to modafinil

2 Table 20: Clinical evidence profile: amantadine compared to modafinil for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	modafinil	Relative (95% CI)	Absolute (95% CI)		
Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value, parallel trial and crossover trial) at 3-6 months (follow up: mean 5 weeks; assessed with: MFIS; Scale from: 0 to 84)												
2	randomised trials	serious [a]	very serious [b]	serious [c]	very serious [d,e]	none	139	139	-	MD **7.51 lower** (27.58 lower to 12.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal due to adverse events at 3-6 months (crossover) (follow up: 6 weeks)												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [e,f]	none	3/127 (2.4%)	1/125 (0.8%)	**RR 2.95** (0.31 to 28.01)	**16 more per 1,000** (from 6 fewer to 216 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cardiac events/arrhythmias at 3-6 months (crossover) (follow up: 6 weeks)												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [e,f]	none	3/127 (2.4%)	5/125 (4.0%)	**RR 0.59** (0.14 to 2.42)	**16 fewer per 1,000** (from 34 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow up: 4 weeks; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [c]	serious [e,g]	none	15	15	-	MD **7.1 lower** (12.21 lower to 1.99 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow up: 4 weeks; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [c]	serious [e,h]	none	15	15	-	MD **6 higher** (1.01 higher to 10.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	modafinil	Relative (95% CI)	Absolute (95% CI)		
Epworth Sleepiness scale (0-24, lower values are better, final value, crossover trial) at 3-6 months (follow up: 6 weeks; assessed with: Epworth Sleepiness scale; Scale from: 0 to 24)												
1	randomised trials	serious [a]	not serious	serious [c]	not serious [i]	none	124	124	-	MD **1 higher** (0.02 higher to 1.98 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 or 2 increments because of outcome indirectness

d. MID = 5.53 (0.5 x median baseline SD)

e. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

f. Imprecision MID = 0.75-1.25 RR. Clinical effectiveness MID = 50 more per 1000.

g. MID = 3.34 (0.5 x control group SD for final value as no baseline values reported)

h. MID = 3.25 (0.5 x control group SD for final value as no baseline values reported)

i. MID = 2.40 (0.5 x median baseline SD)

Amantadine compared to placebo

Table 21: Clinical evidence profile: amantadine compared to placebo for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
Patient-reported outcome measures to assess MS fatigue (FSS, 1-7, lower values are better, change score and final value, parallel trials) at 3-6 months (follow up: mean 2 months; assessed with: FSS; Scale from: 1 to 7)												
2	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	37	37	-	MD **0.56 lower** (0.81 lower to 0.31 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value, parallel trial and crossover trial) at 3-6 months (follow up: mean 5 weeks; assessed with: MFIS; Scale from: 0 to 84)												
3	randomised trials	serious [a]	very serious [e]	serious [b]	very serious [d,f]	none	154	153	-	MD **3.57 lower** (15.06 lower to 7.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - energy level, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - energy level; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,g]	none	22	22	-	MD **0.28 higher** (0.06 higher to 0.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - muscle strength, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - muscle strength; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,g]	none	22	22	-	MD **0.19 higher** (0.03 lower to 0.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - concentration/memory, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - concentration/memory; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,h]	none	22	22	-	MD **0.42 higher** (0.18 higher to 0.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - motivation level, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - motivation level; Scale from: 1 to 5)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,h]	none	22	22	-	MD **0.18 higher** (0.06 lower to 0.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - ability to finish task, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - ability to finish task; Scale from: 1 to 5)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,h]	none	22	22	-	MD **0.14 higher** (0.1 lower to 0.38 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - ability to solve problem, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - ability to solve problem; Scale from: 1 to 5)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,i]	none	22	22	-	MD **0.24 higher** (0.02 lower to 0.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Patient-reported outcome measures to assess MS fatigue (diary ratings of fatigue - wellbeing, 1-5, higher values are better, final values, crossover trial) at 3-6 months (follow up: 10 weeks; assessed with: diary ratings of fatigue - wellbeing; Scale from: 1 to 5)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,j]	none	22	22	-	MD **0.27 higher** (0.07 higher to 0.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Adverse events leading to withdrawal at 3-6 months (parallel trial and crossover trials) (follow up: mean 7 weeks)

7	randomised trials	serious [a]	serious [k]	serious [b]	very serious [l,m]	none	-/370	-/371	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more) [n]	⨁◯◯◯ VERY LOW	CRITICAL

Disruption of sleep at 3-6 months (parallel trial and crossover trial) (follow up: mean 6 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	serious [b]	serious [d,o]	none	36/146 (24.7%)	20/150 (13.3%)	**RR 1.81** (1.11 to 2.94)	**108 more per 1,000** (from 15 more to 259 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cardiac events/arrhythmias at 3-6 months (parallel trial and crossover trials) (follow up: mean 6 weeks)												
3	randomised trials	serious [a]	serious [k]	serious [b]	very serious [l,m]	none	-/273	-/274	**RD 0.00** (-0.01 to 0.02)	**0 fewer per 1,000** (from 10 fewer to 20 more) [n]	⨁◯◯◯ VERY LOW	CRITICAL
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow up: 4 weeks; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [d,p]	none	15	15	-	MD **7.1 lower** (12.21 lower to 1.99 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow up: 4 weeks; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [d,q]	none	15	15	-	MD **8.4 higher** (2.9 higher to 13.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (13-item activities of daily living intellectual function factor, 0-50, lower values are better, final value, crossover trial) at 3-6 months (follow up: 3 weeks; assessed with: 13-item activities of daily living intellectual function factor; Scale from: 0 to 50)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [r]	none	86	86	-	MD **0.58 lower** (1.54 lower to 0.38 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (selective reminding - long-term retrieval, higher values are better, final value) at 3-6 months (follow up: 2 months; assessed with: selective reminding - long-term retrieval)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,s]	none	16	16	-	MD **3 lower** (13.23 lower to 7.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
Cognitive functions (selective reminding - delayed recall, higher values are better, final value) at 3-6 months (follow up: 2 months; assessed with: selective reminding - delayed recall)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [d,t]	none	16	16	-	MD **0** (2.33 lower to 2.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (selective reminding - sum of recall, higher values are better, final value) at 3-6 months (follow up: 2 months; assessed with: selective reminding - sum of recall)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [d,u]	none	16	16	-	MD **1.2 lower** (7.14 lower to 4.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (Benton Visual Retention, lower values are better, final value) at 3-6 months (follow up: 2 months; assessed with: Benton Visual Retention)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,v]	none	16	16	-	MD **1.5 higher** (0.03 higher to 2.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (WAIS-R Digit Span, higher values are better, final value) at 3-6 months (follow up: 2 months; assessed with: WAIS-R Digit Span)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,w]	none	16	16	-	MD **0.9 lower** (3.07 lower to 1.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (Trail Making Test - Part A, lower values are better, final value) at 3-6 months (follow up: 2 months; assessed with: Trail Making Test - Part A)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,x]	none	16	16	-	MD **5.3 lower** (13.64 lower to 3.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (Trail Making Test - Part B, lower values are better, final value) at 3-6 months (follow up: 2 months; assessed with: Trail Making Test - Part B)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,y]	none	16	16	-	MD **14.2 lower** (35.14 lower to 6.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (symbol digit modalities test - written, higher values are better, final value) at 3-6 months (follow up: 2 months; assessed with: symbol digit modalities test - written)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [d,z]	none	16	16	-	MD **2 higher** (8.37 lower to 12.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive functions (symbol digit modalities test - oral, higher values are better, final value) at 3-6 months (follow up: 2 months; assessed with: symbol digit modalities test - oral)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [d,aa]	none	16	16	-	MD **0.5 lower** (13.19 lower to 12.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Psychological symptoms (Beck Depression Inventory, 0-63, lower values are better, final value, crossover trial) at 3-6 months (follow up: 3 weeks; assessed with: Beck Depression Inventory; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [ab]	none	86	86	-	MD **0.25 lower** (2.54 lower to 2.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Epworth Sleepiness scale (0-24, lower values are better, final value, crossover trial) at 3-6 months (follow up: 6 weeks; assessed with: Epworth Sleepiness scale; Scale from: 0 to 24)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious [ac]	none	124	123	-	MD **0.1 lower** (1.08 lower to 0.88 higher)	⨁⨁◯◯ LOW	CRITICAL

1 **CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

2 ## Explanations

3 a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of outcome indirectness

c. MID = 0.56 (0.5 x median baseline SD)

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

f. MID = 6.65 (0.5 x median baseline SD)

g. MID = 0.16 (0.5 x control group SD for final value as no baseline values reported)

h. MID = 0.19 (0.5 x control group SD for final value as no baseline values reported)

i. MID = 0.21 (0.5 x control group SD for final value as no baseline values reported)

j. MID = 0.14 (0.5 x control group SD for final value as no baseline values reported)

k. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

l. MID = 50 per 1000

m. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

n. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

o. Imprecision MID = 0.75 to 1.25. Clinical importance MID = 50 per 1000.

p. MID = 3.98 (0.5 x control group SD for final value as no baseline values reported)

q. MID = 3.34 (0.5 x control group SD for final value as no baseline values reported)

r. MID = 1.58 (0.5 x control group SD for final value as no baseline values reported)

s. MID = 7.35 (0.5 x median baseline SD)

t. MID = 1.43 (0.5 x median baseline SD)

u. MID = 4.25 (0.5 x median baseline SD)

v. MID = 0.60 (0.5 x median baseline SD)

w. MID = 1.55 (0.5 x median baseline SD)

x. MID = 6.53 (0.5 x median baseline SD)

y. MID = 15.53 (0.5 x median baseline SD)

z. MID = 7.20 (0.5 x median baseline SD)

aa. MID = 7.73 (0.5 x median baseline SD)

ab. MID = 3.89 (0.5 x control group SD for final value as no baseline values reported)
ac. MID = 2.70 (0.5 x median baseline SD)

SSRIs compared to placebo

Table 22: Clinical evidence profile: SSRIs compared to placebo for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	placebo	Relative (95% CI)	Absolute (95% CI)		
Patient-reported outcome measures to assess MS fatigue (MFIS, 0-84, lower values are better, final value) at 3-6 months (follow-up: 4 months; assessed with: MFIS; Scale from: 0 to 84)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,d]	none	22	20	-	MD **12.8 lower** (22.93 lower to 2.67 lower)	⨁◯◯◯ Very low	CRITICAL
Patient-reported outcome measures to assess MS fatigue (Modified fatigue impact scale, Neurological Fatigue Index Summary Score [different scale ranges], lower values are better, final values, parallel trials) at >6 months-1 year (follow-up: mean 54 weeks; assessed with: Modified fatigue impact scale, Neurological Fatigue Index Summary Score)												
2	randomised trials	not serious	not serious	not serious	not serious[e]	none	161	167	-	SMD **0.16 higher** (0.06 lower to 0.37 higher)	⨁⨁⨁⨁ High	CRITICAL
Adverse events leading to withdrawal at >6 months-1 year (parallel trial) (follow-up: 60 weeks)[f]												
1	randomised trials	serious[a]	not serious	not serious	very serious[d,g]	none	5/69 (7.2%)	7/68 (10.3%)	**RR 0.70** (0.23 to 2.11)	**31 fewer per 1,000** (from 79 fewer to 114 more)	⨁◯◯◯ Very low	CRITICAL
Disruption to sleep at >6 months-1 year (parallel trial) (follow-up: 60 weeks)[f]												
1	randomised trials	serious[a]	not serious	not serious	not serious[h]	none	1/69 (1.4%)	0/68 (0.0%)	**OR 7.28** (0.14 to 367.07)	**10 more per 1,000** (from 20 fewer to 50 more)[i]	⨁⨁⨁◯ Moderate	CRITICAL
Cardiac events/arrhythmias at >6 months-1 year (parallel trial) (follow-up: 96 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[j]	serious[d,g]	none	3/111 (2.7%)	2/112 (1.8%)	**RR 1.51** (0.26 to 8.88)	**9 more per 1,000** (from 13 fewer to 141 more)	⨁⨁◯◯ Low	CRITICAL
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow-up: 4 months; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[d,k]	none	22	20	-	MD **0.9 higher** (6.87 lower to 8.67 higher)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow-up: 4 months; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[d,l]	none	22	20	-	MD **5.9 higher** (8.25 lower to 20.05 higher)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (EQ-5D-5L utility index score, -0.11-1, higher values are better, final value, parallel trial) at >6 months-1 year (follow-up: 48 weeks; assessed with: EQ-5D-5L utility index score; Scale from: -0.11 to 1)												
1	randomised trials	not serious	not serious	not serious	very serious[d,m]	none	93	101	-	MD **0.01 higher** (0.04 lower to 0.06 higher)	⨁⨁◯◯ Low	CRITICAL
Health-related Quality of Life (EQ-5D-5L visual analogue scale score, 0-100, higher values are better, final value, parallel trial) at >6 months-1 year (follow-up: 48 weeks; assessed with: EQ-5D-5L visual analogue scale score; Scale from: 0 to 100)												
1	randomised trials	not serious	not serious	not serious	not serious[n]	none	93	101	-	MD **3.18 higher** (2.6 lower to 8.96 higher)	⨁⨁⨁⨁ High	CRITICAL
Cognitive functions (PDQ, 0-100, lower values are better, final value, parallel trial) at 3-6 months (follow-up: 4 months; assessed with: PDQ; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[d,o]	none	22	20	-	MD **11.3 lower** (19.1 lower to 3.5 lower)	⨁◯◯◯ Very low	CRITICAL
Cognitive functions (Symbol digit modalities test, higher values are better, final value, parallel trials) at >6 months-1 year (follow-up: mean 54 weeks; assessed with: Symbol digit modalities test)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	not serious[p]	none	161	167	-	MD **0.77 lower** (3.42 lower to 1.88 higher)	⨁⨁⨁⨁ High	CRITICAL
Cognitive functions (California verbal learning test-II, higher values are better, final value, parallel trial) at >6 months-1 year (follow-up: 60 weeks; assessed with: California verbal learning test-II)[f]												
1	randomised trials	serious[a]	not serious	not serious	not serious[q]	none	68	66	-	MD **0.5 higher** (8.98 lower to 9.98 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Cognitive functions (Controlled oral word association test - semantic, higher values are better, final value, parallel trial) at >6 months-1 year (follow-up: 60 weeks; assessed with: Controlled oral word association test - semantic)[f]												
1	randomised trials	serious[a]	not serious	not serious	not serious[r]	none	68	66	-	MD **0.4 higher** (1.63 lower to 2.43 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Cognitive functions (Controlled oral word association test - phonetic, higher values are better, final value, parallel trial) at >6 months-1 year (follow-up: 60 weeks; assessed with: Controlled oral word association test - phonetic)[f]												
1	randomised trials	serious[a]	not serious	not serious	serious[d,s]	none	68	66	-	MD **5.5 higher** (1.54 higher to 9.46 higher)	⨁⨁◯◯ Low	CRITICAL
Psychological symptoms (HAM-D, 0-50, lower values are better, final value, parallel trial) at 3-6 months (follow-up: 4 months; assessed with: HAM-D; Scale from: 0 to 50)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[d,t]	none	22	20	-	MD **4.5 lower** (7.29 lower to 1.71 lower)	⨁◯◯◯ Very low	CRITICAL
Psychological symptoms (Beck depression inventory-II, 0-63, lower values are better, final values, parallel trial) at >6 months-1 year (follow-up: 60 weeks; assessed with: Beck depression inventory-II; Scale from: 0 to 63)[f]												
1	randomised trials	very serious[a]	not serious	not serious	not serious[u]	none	68	66	-	MD **0.6 higher** (2.1 lower to 3.3 higher)	⨁⨁◯◯ Low	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because of population indirectness

c. MID = 6.68 (0.5 x median baseline SD)

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID = 0.5 (based on SMD as this used to combine two different scales)

f. This is not downgraded for indirectness as there was a period of 4 weeks where the fluoxetine dose was titrated up that was included in this follow up period. Therefore, the follow up is essentially 1 year.

g. Imprecision MID = 0.75-1.25. Clinical effectiveness MID = 50 per 1000.

h. MID = 50 per 1000.

i. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

j. Downgraded by 1 or 2 increments due to outcome indirectness

k. MID = 6.15 (0.5 x median baseline SD)

l. MID = 4.90 (0.5 x median baseline SD)

m. MID = 0.03 (pragmatic value agreed between the NICE and the NGC)

n. MID = 9.95 (0.5 x median baseline SD)

o. MID = 7.00 (0.5 x median baseline SD)

p. MID = 5.9 (0.5 x median baseline SD)

q. MID = 14.09 (0.5 x median baseline SD)

r. MID = 3.10 (0.5 x median baseline SD)

s. MID = 7.62 (0.5 x median baseline SD)

t. MID = 2.23 (0.5 x median baseline SD)

u. MID = 4.13 (0.5 x median baseline SD)

Aspirin compared to placebo

Table 23: Clinical evidence profile: aspirin compared to placebo for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	aspirin	placebo	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse events at 3-6 months (parallel trial) (follow up: 8 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,d]	none	5/64 (7.8%)	3/56 (5.4%)	**RR 1.46** (0.36 to 5.83)	**25 more per 1,000** (from 34 fewer to 259 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments due to outcome indirectness

c. Imprecision MID = 0.75-1.25. Clinical importance MID = 50 per 1000.

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 Modafinil compared to placebo

2 Table 24: Clinical evidence profile: modafinil compared to placebo for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modafinil	placebo	Relative (95% CI)	Absolute (95% CI)		
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale Total Score, 0-84, lower values are better, final value, parallel trial and crossover trials) at 3-6 months (follow-up: mean 6 weeks; assessed with: Modified Fatigue Impact Scale Total Score; Scale from: 0 to 84)												
5	randomised trials	serious[a]	not serious	serious[b]	not serious[c]	none	278	271	-	MD **0.23 lower** (2.68 lower to 2.22 higher)	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events (parallel trial and crossover trials) at 3-6 months (follow-up: mean 6 weeks)												
2	randomised trials	not serious	not serious	serious[b]	very serious[d,e]	none	2/143 (1.4%)	2/142 (1.4%)	**RR 1.00** (0.18 to 5.63)	**0 fewer per 1,000** (from 12 fewer to 65 more)	⨁◯◯◯ Very low	CRITICAL
Cardiac events/arrhythmias at 3-6 months (crossover trial) (follow-up: 6 weeks)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[d,e]	none	5/125 (4.0%)	3/124 (2.4%)	**RR 1.65** (0.40 to 6.77)	**16 more per 1,000** (from 15 fewer to 140 more)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (HAQUAMS, scale range unclear, lower values are better, final value, parallel trial) at 3-6 months (follow-up: 8 weeks; assessed with: HAQUAMS)												
1	randomised trials	not serious	not serious	serious[b]	serious[e,f]	none	62	59	-	MD **0.45 higher** (0.59 lower to 1.49 higher)	⨁⨁◯◯ Low	CRITICAL
Health-related Quality of Life (SF-36 physical component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow-up: 4 weeks; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[e,g]	none	15	15	-	MD **1.3 higher** (3.81 lower to 6.41 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modafinil	placebo	Relative (95% CI)	Absolute (95% CI)		
Health-related Quality of Life (SF-36 mental component summary, 0-100, higher values are better, final value, parallel trial) at 3-6 months (follow-up: 4 weeks; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[e,h]	none	15	15	-	MD **2.4 higher** (2.59 lower to 7.39 higher)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Bodily pain, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Multiple Sclerosis Quality of Life Inventory - Bodily pain)												
1	randomised trials	not serious	not serious	serious[b]	very serious[e,i]	none	18	18	-	MD **0** (1.89 lower to 1.89 higher)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Physical functioning, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Multiple Sclerosis Quality of Life Inventory - Physical functioning)												
1	randomised trials	not serious	not serious	serious[b]	not serious[l]	none	18	18	-	MD **6.24 higher** (3.29 higher to 9.19 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - role physical, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Multiple Sclerosis Quality of Life Inventory - role physical)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious[k]	none	18	18	-	MD **2.65 higher** (2.12 higher to 3.18 higher)	⨁⨁◯◯ Low	CRITICAL
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - vitality scale, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Multiple Sclerosis Quality of Life Inventory - vitality scale)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[e,l]	none	18	18	-	MD **4.11 higher** (0.2 higher to 8.02 higher)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - General health, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Multiple Sclerosis Quality of Life Inventory - General health)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modafinil	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[b]	very serious[e,m]	none	18	18	-	MD **0.2 higher** (2.63 lower to 3.03 higher)	⨁◯◯◯ Very low	CRITICAL
Health-related Quality of Life (Multiple Sclerosis Quality of Life Inventory - Mental health, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Multiple Sclerosis Quality of Life Inventory - Mental health)												
1	randomised trials	not serious	not serious	serious[b]	not serious[n]	none	18	18	-	MD **18.54 higher** (16.6 higher to 20.48 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Cognitive functions (Digital Vigilance Test total errors, lower values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Digital Vigilance Test total errors)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[e,o]	none	18	18	-	MD **1.34 lower** (4.22 lower to 1.54 higher)	⨁◯◯◯ Very low	CRITICAL
Cognitive functions (Weschler Adult Intelligence Scale-III Digit Span Total, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Weschler Adult Intelligence Scale-III Digit Span Total)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[e,p]	none	18	18	-	MD **0.63 lower** (3.76 lower to 2.5 higher)	⨁◯◯◯ Very low	CRITICAL
Cognitive functions (Weschler Adult Intelligence Scale-III Letter Number Sequencing, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Weschler Adult Intelligence Scale-III Letter Number Sequencing)												
1	randomised trials	not serious	not serious	serious[b]	very serious[e,q]	none	18	18	-	MD **0.06 lower** (2.35 lower to 2.23 higher)	⨁◯◯◯ Very low	CRITICAL
Cognitive functions (symbol digit modalities test, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: symbol digit modalities test)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[e,r]	none	18	18	-	MD **0.32 lower** (9.5 lower to 8.86 higher)	⨁◯◯◯ Very low	CRITICAL
Cognitive functions (California Verbal Learning Test - Second Edition, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: California Verbal Learning Test - Second Edition)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modafinil	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	very serious[e,s]	none	18	18	-	MD **2.56 lower** (10.9 lower to 5.78 higher)	⨁◯◯◯ Very low	CRITICAL
Psychological symptoms (The State Trait Anxiety Inventory, 0-60, lower values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: The Strate Trait Anxiety Inventory; Scale from: 0 to 60)												
1	randomised trials	not serious	not serious	serious[b]	serious[e,t]	none	18	18	-	MD **1.5 lower** (6.82 lower to 3.82 higher)	⨁⨁◯◯ Low	CRITICAL
Psychological symptoms (Chicago Multiscale Depression Inventory Total Score, scale range unclear, higher values are better, final value, crossover trial) at 3-6 months (follow-up: 2 months; assessed with: Chicago Multiscale Depression Inventory Total Score)												
1	randomised trials	not serious	not serious	serious[b]	very serious[e,u]	none	18	18	-	MD **0.37 higher** (12.01 lower to 12.75 higher)	⨁◯◯◯ Very low	CRITICAL
Epworth Sleepiness scale (0-24, lower values are better, final values, parallel trial and crossover trial) at 3-6 months (follow-up: 7 weeks; assessed with: Epworth Sleepiness scale; Scale from: 0 to 24)												
2	randomised trials	not serious	not serious	serious[b]	not serious[v]	none	186	182	-	MD **0.78 lower** (1.62 lower to 0.07 higher)	⨁⨁⨁◯ Moderate	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments due to outcome indirectness

c. MID = 5.8 (0.5 x median baseline SD)

d. Imprecision MID = 0.75-1.25. Clinical importance MID = 50 per 1000.

e. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

f. MID = 1.24 (0.5 x median baseline SD)

g. MID = 3.79 (0.5 x control group SD for final value as no baseline values reported)

h. MID = 3.70 (0.5 x control group SD for final value as no baseline values reported)

i. MID = 1.45 (0.5 x median baseline SD)

j. MID = 2.39 (0.5 x median baseline SD)

k. MID = 0.41 (0.5 x median baseline SD)

l. MID = 2.83 (0.5 x median baseline SD)

m. MID = 2.16 (0.5 x median baseline SD)

n. MID = 1.90 (0.5 x median baseline SD)

o. MID = 1.02 (0.5 x median baseline SD)

p. MID = 2.04 (0.5 x median baseline SD)

q. MID = 1.10 (0.5 x median baseline SD)

r. MID = 6.32 (0.5 x median baseline SD)

s. MID = 4.73 (0.5 x median baseline SD)

t. MID = 4.10 (0.5 x median baseline SD)

u. MID = 7.74 (0.5 x median baseline SD)

v. MID = 2.5 (0.5 x median baseline SD)

Combination of pharmacological therapies (amantadine and aspirin) compared to amantadine

Table 25: Clinical evidence profile: combination of pharmacological therapies (amantadine and aspirin) compared to amantadine for people with fatigue and multiple sclerosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	combination of pharmacological therapies (amantadine and aspirin)	amantadine	Relative (95% CI)	Absolute (95% CI)		
Patient-reported outcome measures to assess MS fatigue (FSS score, 1-7, lower values are better, final values, parallel trial) at 3-6 months (follow up: 6 weeks; assessed with: FSS score; Scale from: 1 to 7)												
1	randomised trials	not serious	not serious	serious [a]	not serious [b]	none	21	24	-	MD **0.6 lower** (0.89 lower to 0.31 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **MD:** Mean difference

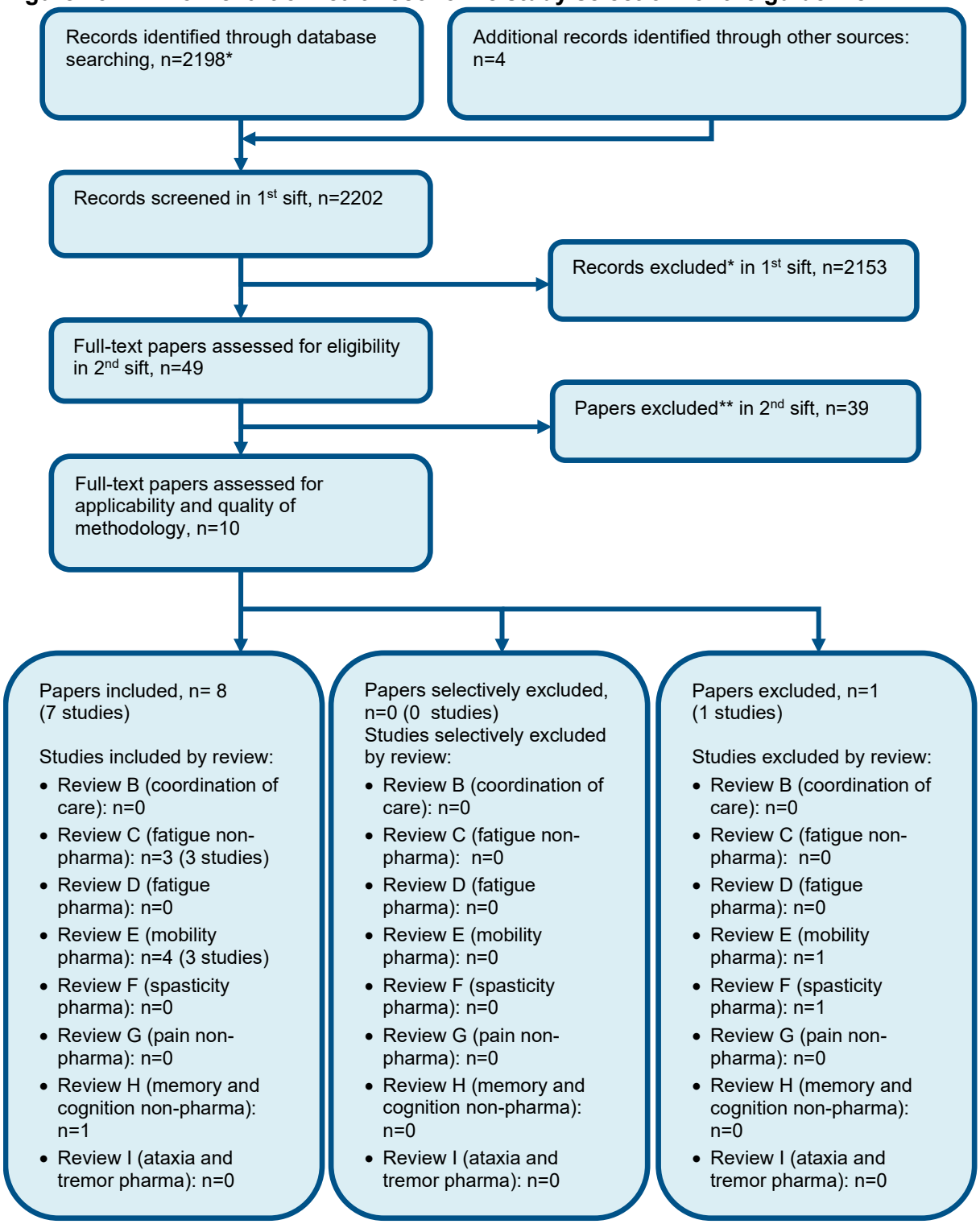
Explanations

a. Downgraded by 1 or 2 increments due to outcome indirectness

b. MID = 0.25 (0.5 x median baseline SD)

Appendix G – Economic evidence study selection

Figure 73: Flow chart of health economic study selection for the guideline



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

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

No original health economic modelling was undertaken as other areas of the guideline were prioritised.

Appendix J – Excluded studies

Clinical studies

Table 26: Studies excluded from the clinical review

Study	Code [Reason]
Asano, Miho and Finlayson, Marcia L. (2014) Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Multiple sclerosis international 2014: 798285	- Systematic review used as source of primary studies
Bazzari, F. H. (2018) Available pharmacological options and symptomatic treatments of multiple sclerosis. Systematic Reviews in Pharmacy 9(1): 17-21	- Review article but not a systematic review
Cameron, M., Cohen, J., Miller, A. et al. (2019) Inroads: A phase 3 study to assess the efficacy and safety of ADS-5102 (Amantadine) extended-release capsules in multiple sclerosis (MS) patients with walking impairment. Neurology 92(15 Suppl 1)	- Conference abstract - Full text paper not available
Chataway, J., De Angelis, F., Connick, P. et al. (2018) MS-SMART Trial: A multi-arm phase 2b randomised double blind, parallel group, placebo-controlled clinical trial comparing the efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis [NCT01910259]. Multiple Sclerosis Journal 24(2 Suppl): 986-987	- Conference abstract
Chen, M. H., Goverover, Y., Genova, H. M. et al. (2020) Cognitive efficacy of pharmacologic treatments in multiple sclerosis: A systematic review. CNS Drugs 34(6): 599-628	- Systematic review used as source of primary studies
Cohen, J. A., Gudesblatt, M., Hunter, S. F. et al. (2017) A phase 2 study of ADS-5102 (amantadine hydrochloride) extended-release capsules in multiple sclerosis patients with walking impairment. Multiple Sclerosis 23(Suppl 1): 22-23	- Conference abstract
Cotter, J., Muhlert, N., Talwar, A. et al. (2018) Examining the effectiveness of acetylcholinesterase inhibitors and stimulant-based medications for cognitive dysfunction in multiple sclerosis: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews 86: 99-107	- Systematic review used as source of primary studies

Study	Code [Reason]
Filippi, M., Valsasina, P., Colombo, B. et al. (2015) Fampridine modulates thalamic resting state functional connectivity and ameliorates fatigue in multiple sclerosis patients. Multiple Sclerosis 23(11 Suppl1): 331-332	- Conference abstract
Khan, F.; Amatya, B.; Galea, M. (2014) Management of fatigue in persons with multiple sclerosis. Frontiers in Neurology 5: 177	- Study does not contain an intervention relevant to this review protocol
Kratz, Anna L., Alschuler, Kevin N., Ehde, Dawn M. et al. (2019) A randomized pragmatic trial of telephone-delivered cognitive behavioral-therapy, modafinil, and combination therapy of both for fatigue in multiple sclerosis: The design of the "COMBO-MS" trial. Contemporary clinical trials 84: 105821	- Data not reported in an extractable format or a format that can be analysed *Protocol only*
Lange R, Volkmer M, Heesen C et al. (2009) Modafinil effects in multiple sclerosis patients with fatigue. Journal of neurology 256(4): 645-650	- Data not reported in an extractable format or a format that can be analysed - Not a peer-reviewed publication
Leavitt, V. M., Blanchard, A. R., Guo, C. Y. et al. (2017) Aspirin improves exercise endurance in multiple sclerosis: Pilot findings from a double-blind randomized placebocontrolled crossover trial. Multiple Sclerosis Journal 23(3 Suppl 1): 413-414	- Conference abstract
Leavitt, V. M., Blanchard, A. R., Guo, C. Y. et al. (2018) Aspirin is an effective pretreatment for exercise in multiple sclerosis: A double-blind randomized controlled pilot trial. Multiple Sclerosis Journal 24(11): 1511-1513	- Study design not relevant to this review protocol *Inadequate washout period*
Leavitt, V., Blanchard, A., Guo, C. Y. et al. (2018) A randomized controlled pilot trial of aspirin to improve exercise performance in persons with multiple sclerosis. Neurology 90(15 Suppl 1)	- Conference abstract - Full text paper not available
Miller, Philippa and Soundy, Andrew (2017) The pharmacological and non-pharmacological interventions for the management of fatigue related multiple sclerosis. Journal of the neurological sciences 381: 41-54	- Study design not relevant to this review protocol *Systematic review of systematic reviews*
Nourbakhsh, B., Revirajan, N., Morris, B. et al. (2019) Phase 3 randomized, controlled trial of	- Conference abstract

Study	Code [Reason]
methylphenidate, modafinil and amantadine for MS fatigue (TRIUMPHANTMS): Baseline data. Multiple Sclerosis Journal 25(Suppl 2): 794-795	
Nourbakhsh, B.; Revirajan, N.; Waubant, E. (2017) Study design for a pragmatic clinical trial of fatigue medications in multiple sclerosis. Neurology 88(16 Suppl 1)	- Conference abstract - Full text paper not available
Payne, C.; Wiffen, P. J.; Martin, S. (2017) Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews 2017(4): cd008427	- Full text paper not available *Withdrawn due to the update not meeting the timelines and expectations of Cochrane and the PaPaS review group*
Perez, Dominique Q.; Espiritu, Adrian I.; Jamora, Roland Dominic G. (2020) Efficacy and safety of amantadine for the treatment of fatigue in multiple sclerosis: a systematic review and meta-analysis. Neurodegenerative disease management 10(6): 383-395	- Systematic review used as source of primary studies
Poulsen, M., Damgaard, B., Zerahn, B. et al. (2015) Feasibility of treatment with modafinil to reduce fatigue after stroke. International Journal of Stroke 10(Suppl 2): 92	- Conference abstract
Rejdak, Konrad and Grieb, Pawel (2020) Adamantanes might be protective from COVID-19 in patients with neurological diseases: multiple sclerosis, parkinsonism and cognitive impairment. Multiple sclerosis and related disorders 42: 102163	- Study design not relevant to this review protocol
Rocca, M. A., Valsasina, P., Colombo, B. et al. (2018) Modulation of cortico-subcortical functional connectivity occurs after symptomatic treatment of fatigue in patients with multiple sclerosis. Multiple Sclerosis Journal 24(Suppl 2): 317-318	- Conference abstract
Rosenberg, G. A. and Appenzeller, O. (1988) Amantadine, fatigue, and multiple sclerosis. Archives of neurology 45(10): 1104-1106	- Primary study from before the date limitation which is unlikely to add extra information that will impact the results of the review
Sailer, M., Heinze, H. J., Schoenfeld, M. A. et al. (2000) Amantadine influences cognitive processing in patients with multiple sclerosis. Pharmacopsychiatry 33(1): 28-37	- Study reported outcomes not included in the protocol (electrophysiological parameters)

Study	Code [Reason]
Santarnecchi, Emiliano, Rossi, Simone, Bartalini, Sabina et al. (2015) Neurophysiological correlates of central fatigue in healthy subjects and multiple sclerosis patients before and after treatment with amantadine. Neural Plasticity 2015: 616242	- Study design not relevant to this review protocol
Shangyan, Hei, Kuiqing, Li, Yumin, Xu et al. (2018) Meta-analysis of the efficacy of modafinil versus placebo in the treatment of multiple sclerosis fatigue. Multiple sclerosis and Related Disorders 19: 85-89	- Systematic review used as source of primary studies
Tsou, A., Treadwell, J., Erinoff, E. et al. (2019) Which treatments improve fatigue and quality of life in Multiple Sclerosis? Evidence appraisal and development of visual interactive evidence maps. Neurology 92(15 Suppl 1)	- Conference abstract - Full text paper not available
Tur, Carmen (2016) Fatigue management in multiple sclerosis. Current Treatment Options in Neurology 18(6): 26	- Review article but not a systematic review
Wingerchuk, D., Keegan, M., Shuster, E. et al. (2014) Aspirin is unlikely to have a clinically meaningful effect on multiple sclerosis-related fatigue: Data from a randomized controlled trial. Neurology 82(10 Suppl 1)	- Conference abstract - Full text paper not available
Wu, S., Kutlubaev, M. A., Chun, H. Y. Y. et al. (2015) Interventions for post-stroke fatigue. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol
Yang, Ting-Ting, Wang, Li, Deng, Xiao-Yang et al. (2017) Pharmacological treatments for fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. Journal of the neurological sciences 380: 256-261	- Systematic review used as source of primary studies
Zielinska-Nowak, E., Wlodarczyk, L., Kostka, J. et al. (2020) New strategies for rehabilitation and pharmacological treatment of fatigue syndrome in multiple sclerosis. Journal of Clinical Medicine 9(11): 1-18	- Systematic review used as source of primary studies

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 27: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

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

K.1.2 Why this is important

Fatigue is a major problem for people with MS. Studies indicate that between 80-90% of all people with MS experience fatigue and up to 40% describe it as the most disabling symptom of the condition. Much is written regarding the effects on daily life including its impact on employment, where fatigue is one of the key factors leading to early retirement. MS fatigue is often described as primary fatigue (directly related to the condition due to causes such as nerve fibre fatigue, heat sensitive fatigue or lassitude) or secondary fatigue, where other factors may worsen the fatigue experienced, such as infection, low mood or environmental challenges. Although medications exist which may reduce fatigue, but further research is needed to identify the benefits and harms of interventions to manage these symptoms.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	If pharmacological Interventions are shown to offer clinically important benefits to the management of fatigue 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. 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 fatigue and support decision making in the development of future recommendations.
Relevance to the NHS	A clear recommendation for the non-pharmacological interventions for fatigue will offer clinicians clearer guidance on best care for people with MS. Increased knowledge of A clear recommendation for the non-pharmacological interventions for memory and cognition will offer clinicians clearer guidance on best care for people with MS. Increased knowledge of non-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	Limited evidence showed a benefit for amantadine, modafinil and SSRIs for the treatment on fatigue. The lack of evidence comparing these different interventions meant

	that the committee were unable to recommend in what order these treatments should be considered. Very limited evidence was found on aspirin. No evidence was identified on combinations of interventions.
Equality considerations	Trials are unlikely to impact on equality issues.

K.1.4 Modified PICO table

Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care, who are experiencing fatigue. Exclusion: Children and young people (≤18 years).
Intervention	• Amantadine • SSRIs • Aspirin specifically before exercise • Modafinil • Combinations of the above
Comparator	Interventions will be compared to each other (both within and between classes), placebo/sham, or usual care.
Outcome	• Patient-reported outcome measures to assess MS fatigue, including MFIS Fatigue Severity Scale (FSS), National Fatigue Index (NFI), MS-specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS), • Visual Analogue Scale (VAS) • Adverse effects of treatment. o Adverse events leading to withdrawal o Disruption of sleep o cardiac events/arrhythmias • Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale. • Impact on patients/carers. • Cognitive functions, such as memory and concentration • Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments. • Epworth sleepiness scale Follow up: • 3-6 months • >6 months – 1 year

Study design	RCT
Timeframe	Medium term
Additional information	Consideration should be given to subgroups in order to explore how people with different clinical characteristics respond to the interventions