New Medicine Assessment

Amantadine for Fatigue in Multiple Sclerosis

Recommendation: Amber 0 for the following indications:

Fatigue in multiple sclerosis.

On advice of neurology only.

Summary of supporting evidence:

- Unlicensed indication, but existing practice.
- Low patient numbers; cost impact anticipated to be low.
- Non-pharmacological options are first-line.
- Recommended by NICE for use in patients whose quality of life is severely affected by fatigue.
- Systematic reviews have shown minimal effectiveness for this indication and in some cases a high incidence of adverse effects. However, they acknowledge the poor quality of studies and short-term nature which may not have illustrated longer term improvements.
- Use is supported by neurology locally. These patients have regular neurology follow up; if the medication is not showing any benefit then it is stopped.
- No routine monitoring required.
- Risk of impulse control disorders.

Details of Review

Name of medicine (generic & brand name)**:**

Amantadine hydrochloride

Strength(s) and form(s):

Capsules 100mg

Oral solution 50mg/5ml

Dose and administration:

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[1]

BNF therapeutic class / mode of action:

Weak dopamine agonist with modest antiparkinsonian effects.

Licensed indication(s):

Parkinson's disease

Herpes zoster (some preparations)

Prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus (some

preparations)

Proposed use (if different from, or in addition to, licensed indication above):

Fatigue in multiple sclerosis (unlicensed indication).

Course and cost:

Amantadine 100mg,56 capsules £5.90

Maintenance dose 100mg-200mg twice daily = £5.90 - £11.80/patient/month

£70.80 - £141.60 /patient/year

Drug tariff price January 2026

Current standard of care/comparator therapies:

NICE NG220: Patients living with MS should be asked if they are experiencing fatigue, sudden tiredness or a change in their energy levels affecting their daily living. If so, they should be offered advice on non-pharmacological management of fatigue:[2]

- Advice on conserving energy
- Diet and exercise
- Stress management and wellbeing approaches such as mindfulness and cognitive behavioural techniques to help with day-to-day activities.
- Aerobic, resistive and balance exercises, including yoga and pilates

Pharmacological options include (unlicensed indications)[2]:

- Amantadine
- Modafinil (except in people who are pregnant or planning pregnancy)
- SSRIs

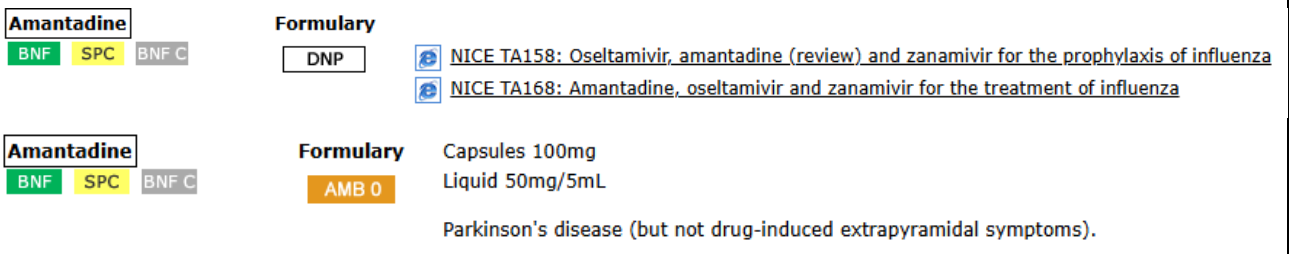
Relevant NICE guidance:

NG220: Multiple sclerosis in adults: management

Background and context

Fatigue is one of the most common and disabling symptoms of people with Multiple Sclerosis (MS). The effective management of fatigue has an important impact on the patient's functioning, abilities, and quality of life. Although a number of strategies have been devised for reducing fatigue, treatment recommendations are based on a limited amount of scientific evidence.[6]

Current formulary entries for amantadine:



Current formulary entry for modafinil:

Modafinil	Formulary	Tablets 100mg
BNF SPC BNF C	AMB 0	Specialist initiation only.

Summary of evidence

Summary of efficacy data in proposed use:

NICE[2](2024)

The evidence for treating fatigue with amantadine, modafinil or selective serotonin reuptake inhibitors (SSRIs) in people with MS was limited but showed some benefit for each medicine. The lack of good evidence comparing the different treatments meant that the committee were unable to recommend one in preference to the others or an order in which these treatments should be considered. However, they agreed that fatigue can have a significant impact on the person's daily activities and that, in their clinical experience, it can improve with pharmacological treatment in some people. Amantadine, modafinil and SSRIs are not licensed for treating fatigue in people with MS and there are safety issues associated with their use, so they should only be started by a specialist in MS.

The committee agreed that the potential benefits of effective treatment may outweigh the risks for people whose quality of life is severely affected by fatigue. However, they highlighted that people with MS should be fully informed about the possible risks and benefits, and make a shared decision with a specialist about whether to try a medicine and which would be most suitable, taking into account their needs, priorities and preferences. They agreed that it is important that people can access pharmacological treatment options and that they can be considered before trying non-pharmacological treatments in people for whom a rapid response is a priority.

The committee highlighted the particular safety concerns for modafinil, including that it should not be used by people who are pregnant or planning pregnancy, and that precautions should be taken if prescribing it for people able to get pregnant.

The committee noted additional advice for modafinil on monitoring, stopping treatment and cautions for use in the 2014 MHRA safety advice on modafinil and advice in the summary of product characteristics for modafinil and amantadine. Based on their experience, the committee highlighted the importance of starting people on a low dose of modafinil, such as 100 mg once a day. The committee agreed that people taking these medicines would need to have regular reviews to monitor effectiveness and safety, adjust dosages and ensure that treatment is stopped if it is ineffective or the person experiences adverse effects. If treatment is effective and the person is on a stable dose of their medicine, the committee agreed that responsibility for prescribing could be transferred to primary care under a shared-care arrangement.

Systematic review and meta-analysis[3] (2025)

Of 259 screened studies, 16 met the inclusion criteria for this review. Standardised mean differences showed a change of -0.26 (95 % CI, -0.54, 0.01) in the direction of medications (amantadine, modafinil, methylphenidate, and 4-aminopyridine), representing a decrease of 0.29 in Fatigue Severity Scale (FSS) or 3.90 in Modified Fatigue Impact Scale (MFIS) (minimally important difference is 0.45 for FSS and 4 for MFIS). The pooled risk ratio for discontinuation was 2.11 (95 % CI, 1.19, 3.77), favouring controls. The subgroup analysis focused on amantadine did not support its efficacy for reducing fatigue (SMD − 0.27, 95 % CI, − 0.88, 0.35). Most studies were without substantial risk of bias, but the certainty of evidence was low. The studied medications have minimal to no efficacy and an uncertain clinical significance in reducing fatigue in persons with multiple sclerosis.

Systematic Review and Meta-analysis[4] (2025)

Systematic review and meta-analysis to evaluate the effectiveness of amantadine in the management of patients with multiple sclerosis-related fatigue (MSRF). Primary objective was to assess its effectiveness, while the secondary objective was to evaluate adverse effect patterns.

Included 9 RCTs, with a total of 601 patients, of whom 66% received amantadine. There was no statistically significant reduction in fatigue severity in patients treated with amantadine compared to placebo (SMD −0.22; 95% CI [−0.72, −0.27]; P = 0.37; I^2 = 66%). Notably, amantadine treatment was associated with higher odds of experiencing insomnia (OR 2.33; 95% CI [1.26, 4.28]; P = 0.006; I^2 = 0%). The results of this meta-analysis suggest that amantadine is not effective in treating MSRF and is associated with a higher

likelihood of adverse effects.

Randomised, placebo-controlled, crossover, double-blind trial[5] (2023)

Randomised, placebo-controlled, four-sequence, four-period, crossover, double-blind trial, patients with multiple sclerosis who reported fatigue and had a Modified Fatigue Impact Scale (MFIS) score of more than 33 were recruited at two academic multiple sclerosis centres in the USA. Participants received oral amantadine (up to 100 mg twice daily), modafinil (up to 100 mg twice daily), methylphenidate (up to 10 mg twice daily), or placebo, each given for up to 6 weeks. All patients were intended to receive all four study medications, in turn, in one of four different sequences with 2-week washout periods between medications.

The primary outcome measure was the MFIS measured while taking the highest tolerated dose at week 5 of each medication period, analysed by use of a linear mixed-effect regression model.

Data from 136 participants were available for the intention-to-treat analysis of the primary outcome. The estimated mean values of MFIS total scores at baseline and the maximal tolerated dose were as follows: 51·3 (95% CI 49·0–53·6) at baseline, 40·6 (38·2–43·1) with placebo, 41·3 (38·8–43·7) with amantadine, 39·0 (36·6–41·4) with modafinil, and 38·6 (36·2–41·0) with methylphenidate (p=0·20 for the overall medication effect in the linear mixed-effect regression model).

As compared with placebo (38 [31%] of 124 patients), higher proportions of participants reported adverse events while taking amantadine (49 [39%] of 127 patients), modafinil (50 [40%] of 125 patients), and methylphenidate (51 [40%] of 129 patients). Three serious adverse events occurred during the study (pulmonary embolism and myocarditis while taking amantadine, and a multiple sclerosis exacerbation requiring hospital admission while taking modafinil).

Amantadine, modafinil, and methylphenidate were not superior to placebo in improving multiple sclerosis fatigue and caused more frequent adverse events. The results of this study do not support an indiscriminate use of amantadine, modafinil, or methylphenidate for the treatment of fatigue in multiple sclerosis.

The crossover study design might have resulted in a carry-over effect that could not be adequately controlled in the statistical models. The fluctuation of fatigue levels during the study would have created nondifferential misclassification of outcome, which could have biased the results toward the null (no medication effect). The results are applicable only to the short-term impact of the studied medications on fatigue in MS. Because of the limits on drug dose and the short treatment period, we cannot rule out that the results might have been different with long-term use and higher doses of study drugs

Cochrane: Amantadine for fatigue in multiple sclerosis[6] (2007)

Out of 13 pertinent publications, 5 trials met the criteria for inclusion in this review: one study was a parallel arms study, and 4 were crossover trials. The number of randomised participants ranged between 10 and 115, and a total of 272 MS patients were studied. Overall the quality of the studies considered was poor and all trials were open to bias. All studies reported small and inconsistent improvements in fatigue, whereas the clinical relevance of these findings and the impact on patient's functioning and health related quality of life remained undetermined. The number of participants reporting side effects during amantadine therapy ranged from 10% to 57%.

Local specialist feedback – Neurology, LTHTr

"*Some patients do benefit from Amantadine, particularly given how disabling fatigue can be in this patient population.*

It should however be initiated on the recommendation of a specialist and then primary care colleagues can then continue it - these patients have a planned follow up with Neurology service."

Summary of safety data:

Summary of product characteristics[7]

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Individuals subject to convulsions
- A history of gastric ulceration
- Severe renal disease

- Pregnancy

Special warnings and precautions for use

- Patients with confusional or hallucinatory states or underlying psychiatric disorders
- Patients with liver or kidney disorders
- History of cardiovascular disorders
- Abrupt discontinuation of amantadine may result in worsening of Parkinsonism or in symptoms resembling neuroleptic malignant syndrome (NMS), as well as in cognitive manifestations (e.g. catatonia, confusion, disorientation, worsening of mental status, delirium)
- Amantadine should not be stopped abruptly in patients who are treated concurrently with neuroleptics
- As some individuals have attempted suicide with amantadine, prescriptions should be written for the smallest quantity consistent with good patient management
- Should not be given to patients with untreated angle closure glaucoma
- Patients should be regularly monitored for the development of impulse control disorders

Interaction with other medicinal products and other forms of interaction

- Concurrent administration of amantadine and anticholinergic agents or levodopa may increase confusion, hallucinations, nightmares, gastro-intestinal disturbances, or other atropine-like side effects
- In isolated cases, worsening of psychotic symptoms has been reported in patients receiving amantadine and concomitant neuroleptic medication
- Concurrent administration of amantadine and drugs or substances (e.g. alcohol) acting on the CNS may result in additive CNS toxicity.

Undesirable effects

Amantadine's undesirable effects are often mild and transient, usually appearing within the first 2 to 4 days of treatment and promptly disappearing 24 to 48 hours after discontinuation. A direct relationship between dose and incidence of side effects has not been demonstrated, although there seems to be a tendency towards more frequent undesirable effects (particularly affecting the CNS) with increasing doses.

For a comprehensive list of the undesirable effects of amantadine please see product SPC.

Strengths and limitations of the evidence:

Weak trial data to support the use of amantadine for this indication. However, there is local experience of its use in this small cohort of patients with limited available treatment options. Adverse effects may limit its use.

Summary of evidence on cost effectiveness:

Cost effectiveness review for this indication not found.

Prescribing and risk management issues:

No routine monitoring. Adverse effects may be problematic, however patients will be under the care of neurology.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
There are limited pharmacological options for this patient cohort. Fatigue in MS can be disabling, with a large impact on quality of life and ability to function.
Financial implications of the intervention:

The MS society estimates that there are 123 442 people in England living with MS (1 in every 450 people).

There are over 7,100 people newly diagnosed each year in the UK.

Based on a population of 1.8 million people in Lancashire and South Cumbria this equates to approximately 4000 existing MS patients. And approximately 185 new diagnosis every year.

Given that the use of amantadine for fatigue in MS is existing practice and in NICE guidance we anticipate a negligible new cost pressure from the existing population of patients living from MS.

Amantadine is a last line option for this indication, alongside other drug options, so new patient numbers are anticipated to be low. Based on 10% of newly diagnosed MS patients eventually requiring amantadine, this would equate to a cost increase of £2700 annually (although it would likely be lower as this does not accounting for natural attrition of patients receiving the medication).

Service Impact Issues Identified:

No service impact anticipated as this is existing practice.

Equality and Inclusion Issues Identified:

None identified.

Cross Border Issues Identified:

GMMMG have amantadine as RAG **SA** (Green following specialist advice. Drugs that are suitable for initiation by primary care following written or verbal advice from a specialist service. Little or no monitoring is required). No indications listed.

Cheshire and Merseyside have amantadine as RAG **AR** (Amber Recommended requires specialist assessment and recommendation to GP to prescribe in Primary Care). They include the text: *NICE recommends offering amantadine to treat fatigue in people with multiple sclerosis (off-label indication).*

Legal Issues Identified:

None identified.

Media/ Public Interest:

None identified.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] British National Formulary, 'Amantadine hydrochloride' [Accessed January 2026]

[2] National Institute for Health and Care Excellence, 'Multiple sclerosis in adults: management', June 2022. Available: https://www.nice.org.uk/guidance/ng220

[3] Toljan K et al, 'Efficacy of pharmacologic treatments for fatigue in multiple sclerosis: A systematic review and meta-analysis', *Multiple Sclerosis and Related Disorders*, Vol. 96, 2025

[4] Cruccioli M et al, 'Amantadine for Multiple Sclerosis-related Fatigue: A Systematic Review and Meta-analysis of Randomized Controlled Trials', *Neurology*, vol. 104, 2025

[5] Nourbakhsh B 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*, Vol. 20(1), pp 38 – 48. 2023

[6] Pucci E et al, 'Amantadine for fatigue in multiple sclerosis', *Cochrane Database of Systematic Reviews,* 2007 [Accessed January 2026]

[7] Summary of Product Characteristics, 'Amantadine hydrochloride 100 mg Capsules', 2025 [Accessed January 2026]