BMJ Open

Amantadine and/or transcranial magnetic stimulation for fatigue associated with multiple sclerosis (FETEM): study protocol for a phase 3 randomised, double-blind, cross-over, controlled clinical trial

Jordi A Matias-Guiu,[1] Javier González-Rosa,[2,3] Miguel Ángel Hernández,[4] Maria Luisa Martínez-Ginés,[5] Antonio Portolés,[6,7] Natalia Pérez-Macías,[7] Julián Benito-León,[8] Iván Padrón,[9] Julio Prieto,[10] Jorge Matias-Guiu [1]

To cite: Matias-Guiu JA, González-Rosa J, Hernández MÁ, *et al*. Amantadine and/or transcranial magnetic stimulation for fatigue associated with multiple sclerosis (FETEM): study protocol for a phase 3 randomised, double-blind, cross-over, controlled clinical trial. *BMJ Open* 2024;**14**:e078661. doi:10.1136/bmjopen-2023-078661

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-078661).

Received 08 August 2023
Accepted 18 December 2023

For numbered affiliations see end of article.

Correspondence to
Jordi A Matias-Guiu;
jordi.matias-guiu@salud.madrid.org

ABSTRACT

Introduction Fatigue is one of the most disabling symptoms of multiple sclerosis (MS), and effective treatments are lacking. Amantadine is one of the most used treatments, although its efficacy is under debate. Transcranial magnetic stimulation (TMS) is a promising intervention that has shown positive effects in some preliminary investigations. We aim to investigate the effect of 6 weeks of amantadine and/or TMS in fatigue due to MS.

Methods and analysis The study is a national, multicentre, phase 3, randomised, double-blind, cross-over, placebo-controlled and sham-controlled clinical trial. Adult patients with relapsing-remitting MS, Expanded Disability Status Scale score of 1.5–4.5 and Fatigue Severity Score>4 are eligible for the trial. Participants will be randomised to one of the sequences of the study. Each sequence consists of four periods of 6 weeks of treatment and three washout periods of 12–18 weeks. All patients will receive all the combinations of therapies. The primary outcome is the Modified Fatigue Impact Scale. The secondary outcomes are the Symbol Digit Modalities Test (cognition), Beck Depression Inventory-II (depressive symptoms) and Short-Survey 12 (quality of life). Safety and cost-effectiveness will also be evaluated. An exploratory substudy including MRI and blood biomarkers will be conducted.

Ethics and dissemination The study is approved by the Ethics Committee of the Hospital Clinico San Carlos and the Spanish Agency of Medications and Medical Devices. All study findings will be published in scientific peer-reviewed journals and presented at relevant scientific conferences.

Trial registration number EudraCT 2021-004868-95; NCT05809414.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Double-blind, crossover and placebo-controlled and sham-controlled design.
⇒ Transcranial magnetic stimulation will use intermittent theta burst protocol.
⇒ Combination between transcranial magnetic stimulation and amantadine will be tested.
⇒ Safety and cost-effectiveness will also be considered in interpreting the results.
⇒ A limitation is the relatively long-term duration of the participation in the trial and the need for periods with no treatment.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that produces inflammation, demyelination, axonal damage and neurodegeneration. Fatigue is one of the most frequent and disabling symptoms of MS, which is the first cause of non-traumatic disability in people younger than 55 years. Fatigue is a subjective feeling of tiredness or exhaustion, having a physical and mental component that interferes with usual activities. Several studies have associated fatigue with quality-of-life disruption, working difficulties, and economic burden.[1]

In the last years, several high-efficacy disease-modifying therapies have been developed.[2] However, effective treatments for fatigue are lacking. Fatigue is a complex symptom that comprises several physiological and psychological factors, and arises from interoceptive networks involved in the regulation of homeostasis.[3 4] Fatigue perception is estimated subjectively by the patients according to their past capacity to perform several tasks and is measured using standardised questionnaires. Conversely, objective fatigability concerns the change in the performance of a specific task.[4–6] Thus, central and peripheral

mechanisms may be implicated. In MS, cortico-striatal dysfunction and glutamatergic and dopaminergic systems have been involved in the pathophysiology of fatigue.[7 8] Functional connectivity studies have shown the striatum, dorsolateral prefrontal cortex, insula and ventromedial prefrontal cortex as the hubs of the fatigue network.[9] Depression, other neuropsychiatric symptoms (stress, anxiety) and pain may also act as important contributors and modulators of fatigue severity.[4]

There are no approved treatments, although several pharmacological and non-pharmacological interventions have been proposed. Amantadine is one of the most recommended and used treatments, although its efficacy is controversial. Amantadine is an antiviral drug with a weak non-competitive antagonistic effect of the N-methyl-D-aspartate receptors, increasing dopamine release. The effect on fatigue seems mediated by its dopaminergic effects. Meta-analyses have concluded that good-quality randomised clinical trials are needed.[10 11] Recently, a randomised cross-over clinical trial investigating the efficacy of amantadine, modafinil and methylphenidate against placebo showed no significant effects on MS fatigue.[12]

A promising option for fatigue treatment is based on the use of non-invasive brain stimulation techniques. Recent studies have found positive results, although evidence is still limited and large, randomised and controlled clinical trials are necessary.[13–15] Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that has shown positive effects in several neurological and psychiatric conditions by modulating cortical excitability.[16] A new protocol of TMS known as theta burst has been proposed.[17] This protocol is faster, safe and excellently tolerated. Intermittent Theta Burst stimulation produces excitatory effects and has demonstrated non-inferiority to traditional repetitive TMS protocols.[18] This suggests a more straightforward implementation in clinical practice, in which the availability of TMS equipments and personnel is an important restriction.

In this study, our main hypothesis is that TMS and/or amantadine may improve fatigue in MS after 6 weeks of treatment compared with placebo. We present the protocol of a multicentre clinical trial to evaluate the change in the severity of fatigue in patients with MS that will undergo amantadine, TMS and both, in comparison with placebo. We will conduct a randomised, cross-over, double-blind, placebo-controlled and sham-controlled, clinical trial. As secondary endpoints, we will assess changes in cognition, depression and quality of life. This trial will inform about the effectiveness of these interventions. In addition, we will evaluate safety and cost-effectiveness.

METHODS AND ANALYSIS

Study design and setting

The present study is a national, multicentre, randomised, double-blind, cross-over, placebo-controlled and sham-controlled clinical trial. The study is carried out at four centres in Spain, and five centres participate in the recruitment. The study is currently ongoing. The first patient was enrolled in February 2023. We plan that recruitment will be completed by June 2024 and the last participant will complete the trial by December 2025.

Participants

Inclusion criteria

Patients must comply all of the following inclusion criteria: (1) diagnosis of MS (relapsing-remitting form) according to 2017 McDonald criteria;[19] (2) age of at least 18 years old; (3) Expanded Disability Status Scale (EDSS) 1.5–4.5 at the moment of the recruitment; (4) Fatigue Severity Scale>4 (mean score of all items); (5) Beck Depression Inventory-II<30; (6) no history of disease relapses in the previous 3 months; (7) washout period of at least 4 weeks for the following drugs potentially associated with fatigue: amantadine, modafinil, methylphenidate, acetyl-L-carnitine, cannabinol and derivatives, fampridine.

Exclusion criteria

Patients should not meet any of the following exclusion criteria: (1) another disorder beyond MS potentially associated with fatigue (sleep apnea, other autoimmune disorders, chronic fatigue syndrome, poorly controlled arterial hypertension or cardiac failure with NYHA 3–4); (2) secondary epilepsy; (3) any contraindication to amantadine or TMS (hypersensitivity to amantadine, kidney failure, closed-angle glaucoma, history of epilepsy, magnetic-sensitive objects in the head or close to the coil (12 inches); (4) pregnancy, breastfeeding or plans for pregnancy; (5) terminal disorder with less than 1 year of life expectancy; (6) cancer or malignancy in the last 3 years; (7) planning for surgery during the time of the trial; (8) any condition that could challenge the participation and/or follow-up during the trial; (9) alcohol abuse or other toxics in the last year; (10) major psychiatric disorders (eg, schizophrenia, bipolar disorder, etc); (11) inability to communicate, poor use of Spanish or cognitive impairment difficulting the performance of the assessments and the trial; (12) participation in another clinical trial with any drug in the previous 4 months before the patient's inclusion and (13) chronic use of drugs that may impact the results (antiepileptic drugs, benzodiazepines, baclofen, selective serotonin reuptake inhibitors and drugs lowering convulsive threshold) are permitted at stable doses in the previous 3 months before the patient's inclusion.

Recruitment

Patients will be recruited from the Departments of Neurology (MS Units) of Hospital Clinico San Carlos, Hospital Gregorio Marañón, Hospital '12 de Octubre', Hospital Puerta del Mar and Hospital Nuestra Señora de la Candelaria. Patients will be provided with the Informed Consent Form by study staff to review prior to signing the form at their baseline visit with study staff. The sponsor of

the study is the Biomedical Research Foundation of the Hospital Clinico San Carlos.

Withdrawal criteria

Any patient will be withdrawn from the study if any of the following criteria: (1) any condition interrupting the study procedures; (2) development of severe depression; (3) decision of the patient; (4) any serious adverse event associated with treatments used in the study; (5) cancer chemotherapy; (6) pregnancy; (7) need of a prohibited medication (amantadine, modafinil, methylphenidate, acetyl-L-carnitine, cannabidiol, fampridine and chemotherapy) and (8) meeting during the study of exclusion criteria. The development of a disease relapse is not considered a withdrawal criterion. In case of early withdrawal, the investigator team at each site will try to determine the reason and register it.

Sample size calculation

One hundred and forty-four patients will be enrolled. According to previous studies, a change of at least 10 points in Modified Fatigue Impact Scale (MFIS) is considered as clinically significant.[20] Assuming a power of 90%, a type I error of 0.05 corrected by Bonferroni (six comparisons) and an intraclass correlation coefficient of 0.7, we would need 91 patients to detect a difference of at least 10 points between placebo and the interventions. Considering the duration and number of periods of the study, a 20% of loss to follow-up has been estimated, pointing a sample size of at least 136. We have increased the sample to 144 to allow the same number of patients per any of the 24 sequences of the four combinations of treatments (TMS+amantadine/TMS+placebo/sham-TMS+amantadine/shamTMS+placebo) required for a full randomisation scheme.

Interventions

All patients will be treated with TMS and amantadine during the study. Both treatments will be administered in monotherapy and in combination. All patients will receive all the combinations (eg, TMS and placebo; TMS and amantadine; sham TMS and amantadine and sham TMS and placebo), and the only difference will be the sequence of administration (figure 1). Periods of treatment last 6 weeks, and each treatment period will be followed by a washout period of 12–18 weeks to ensure that TMS and amantadine effects are removed. This washout period is considered enough to remove the effects of amantadine and TMS. This implies that the total study duration for each participant will range between 60 and 78 weeks, which may be a significant limitation in terms of patient compliance.

Amantadine

Patients will start with 100 mg one capsule per day for 1 week followed by two capsules per day for 5 weeks. After completing the 6 weeks of the treatment, the patient will take 1 capsule for 5 days before withdrawal. If adverse events occur, dose will be reduced to one capsule per day and this dose will be considered therapeutic. Placebo will have the same size, form, colour and taste and the posology will be identical. Study medications will be delivered to the patient before each treatment period. After each period, the patient will have to return the medication boxes.

Transcranial magnetic stimulation

Intermittent theta-burst protocol (10 triplet bursts at 50 Hz, cycle time of 10 s, 600 pulses) will be used over the left prefrontal dorsolateral cortex. Treatments will be delivered at 120% of the resting motor threshold, with a maximum of 50% of the maximum stimulator output. All sessions will be conducted using a Magstim Rapid2 stimulator (Magstim, Whitland, UK) with an air-cooled figure-of-eight coil and under neuronavigation (Brainsight V.2.4.11). All the centres have the same TMS equipment and will follow the same procedure. MRI of each patient will be used during neuronavigation to provide a more accurate target localisation and treatment.[21] During

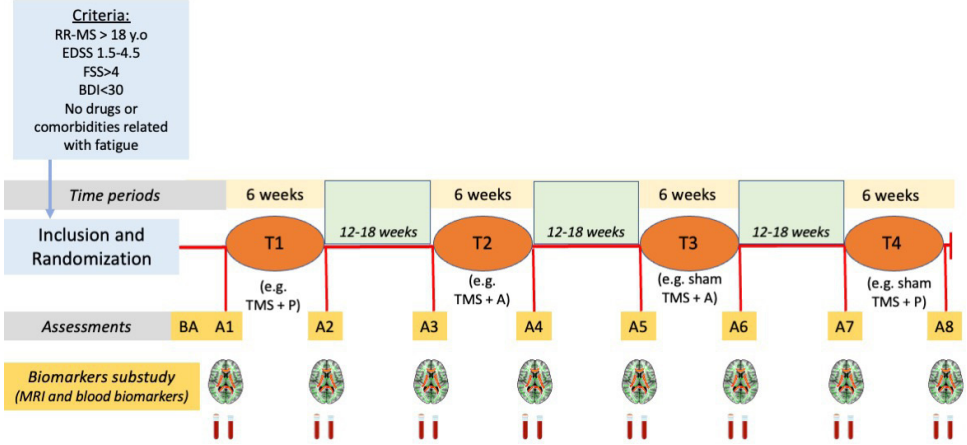

Figure 1 Summary of the trial. A, amantadine; Axe, assessment (1, 2…); BA, baseline assessment; BDI, Beck Depression Inventory; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Score; P, placebo; RR-MS, relapsing-remitting multiple sclerosis; T, treatment period; TMS, transcranial magnetic stimulation.

Table 1 Schedule of assessments

	Baseline visit	Visits 1–8§¶**
Inclusion and exclusion criteria	X	
Patient information/consent	X	
Blood laboratory analysis*	X	
Pregnancy test†	X	
Clinical information‡	X	
Randomisation	X	
MFIS		X
SDMT		X
BDI-II		X
SF-12		X
Concomitant medication	X	X
Entrega/revisión diario de paciente	X	X
Register of disease relapses		X
Adverse events assessment		X

*Laboratory blood analysis will be conducted in patients with endocrine autoimmune disorders in case there are no previous assessments in the last 6 months to confirm the inclusion and exclusion criteria.
†Pregnancy tests will be collected in case of doubt.
‡Date of birth, sex, years of formal education, year of diagnosis of MS, EDSS, FSS and comorbidities.
§Treatment will be started 0–30 days after the baseline visit.
¶Before the onset and after the end of each period (±2 days). Visit 8 is the last study visit.
**Treatment periods last 6 weeks. Washout periods between treatments are 12–18 weeks.
BDI-II, Beck Depression Inventory-Second Edition; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Score; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test; SF-12, Short-Form survey 12.

the treatment periods, patients will receive three sessions per week during 6 weeks (a total of 18 sessions and 10 800 pulses in each period). In the case of sham-stimulation, the procedure will be the same but a sham-coil will be used. Sham coil is probably the more appropriate technique to blind the magnetic stimulation effects.[22] TMS will be applied by technicians specifically trained for the protocol of the study.

Study process

The screening visit includes the patient information, collection of the informed consent form and checking inclusion and exclusion criteria by a neurologist. EDSS and Fatigue Severity Scale will be administered by the same neurologist.[23 24] In the visits 1–8, the patient is evaluated by a trained rater, who is responsible to administer the primary and secondary outcomes (table 1).

Randomisation

Patients will be randomised with a computer-based algorithm (random allocation software) and allocated to one of the 24 treatment sequences. The timing between randomisation and the start of treatment is between 0 and 30 days.

Blinding

Outcome raters and patients will be blinded to treatment. Only the technicians delivering TMS will be aware of the treatment assignment regarding brain stimulation, but not the medication. Just after the randomisation, the technician responsible for the treatment will receive an e-mail informing about the sequence of treatment.

Concomitant treatments during the study

There are no prohibited medications during the clinical trial except for baclofen, chemotherapy and drugs with a potential effect on fatigue (modafinil, fampridine, cannabinol and methylphenidate). Regarding corticosteroids, they will be permitted in topical and inhaled formulations. If oral route is necessary, they will be permitted for acute periods (less than 15 days). Chronic treatments are permitted if the prednisone dose is not superior to 10 mg/day (or equivalent doses in case other corticosteroid is used).

Women before menopause must use effective contraception measures.

Management of disease relapses

Management of relapses is not a criterion for withdrawal. If a relapse needs treatment, we will use methylprednisolone 1 g/day for 3 days. If longer treatment is needed, the patient will be removed from the study.

Assessments

Sociodemographic variables will be documented during the screening visit. Clinical outcomes will be assessed before and after each period of treatment.

Sociodemographic and medical variables

The following variables are registered: age, sex, country of origin, ethnicity and race, years of formal schooling, year of MS symptom onset, smoking habit, medications and comorbidities.

Primary outcome

The primary outcome is the change in the MFIS.[20 25] We will compare the MFIS at the end of each treatment period with the MFIS score obtained just before the start of each period. The MFIS is a self-reported scale of fatigue that contains 21 items assessing cognitive (10 items), physical (nine items) and psychosocial (two items) domains. Each item is scored on a five-point Likert-type scale from 'never' (0 points) to 'most of the time' (four points). The scale ranges from 0 to 84 points, and higher scores mean a higher impact of fatigue.

Secondary outcomes

Secondary outcomes include the change in cognition (using the Symbol Digit Modalities Test (SDMT),[26] depressive symptoms (using the Beck Depression Inventory second version)[27] and quality of life (using the

Short-Form survey 12, SF-12).[28] In all cases, the scores after the end of each treatment period will be compared with those obtained right before the start of that period.

The SDMT is the most used test in MS and has been extensively used for cognitive screening and monitoring in clinical practice and research.[29] This test evaluates attention, visual tracking, processing speed and memory. The patient is asked to transcribe a code of meaningless geometric designs, each one paired with a number. In this study, we will use the oral version, which has been recommended in MS.[29]

The BDI-II is a 21-item questionnaire that evaluates and quantifies the severity of depressive symptoms in adults. It has been validated in MS.[30] Scores range from 0 to 63, and higher scores mean higher severity of depressive symptoms.

The SF-12 is a self-reported measure that evaluates the impact of health on everyday life, and is considered a measure of the quality of life. The scale evaluates limitations in physical, social and usual role activities, bodily pain, general mental health, vitality and general health perception.

Safety assessment

All the investigators (technicians delivering TMS, neurologists and raters) will inquire about adverse events during the visits. We will use the following definitions: (1) an 'adverse event' is defined as any detrimental incidence in a patient participating in a clinical trial with a drug or a medical device. This event may have a causal relationship with the intervention or not; (2) an 'adverse reaction' is defined as any harmful and unintentional reaction, independently from the administered dose. There is a suspicion of a causal relationship with the intervention.

Adverse events or reactions will be considered serious when the patient outcome is death, life-threatening, hospitalisation, disability or permanent damage, require intervention to prevent permanent impairment or damage, or develop a congenital anomaly or disability. Even not meeting the previous criteria, events and reactions will be considered serious when they may jeopardise the patient or require any intervention to prevent one of the previous outcomes.

Causality will be classified as follows: (1) related to the intervention (there is a temporal association and cannot be explained by other factors such as clinical status, comorbidities or other interventions); (2) not-related to the intervention (temporal relationship is improbable, other factors provide a satisfactory explanation). Adverse effects will also be rated as mild (when they do not cause any limitation in daily living activities), moderate (when they cause any limitation) and severe (when they prevent the patient from doing their normal activities).

Furthermore, adverse effects will be classified as expected or non-expected, according to the safety data sheet of amantadine and TMS.

A Data and Safety Monitoring Board (DSMB) comprises five neurologists of recognised expertise working in clinical neurology and MS from five different centres and with no conflicts of interest. This Board will review recruitment status and withdrawals, adverse events and protect the safety of the study participants. They will elaborate preliminary annual and final reports regarding safety and data quality. At least eight meetings will be conducted during the trial duration according to the state of the recruitment and patient completion of the different treatment periods. Additional meetings could be appointed by request of any member of the Board, researcher or sponsor to evaluate safety issues. A majority vote will accord recommendations of the DSMB.

Exploratory substudy with blood biomarkers and MRI

A subgroup of 50 participants from one centre will be invited to undergo a substudy, including MRI and blood biomarkers, at the time of each assessment. These biomarkers will provide insights about potential mechanisms associated with changes induced by each treatment in fatigue severity. Blood samples will be collected before and after each period of treatment, and serum (18 mL) and plasma samples (18 mL) will be stored at −80°C. Samples will be measured using the Quanterix Simoa technology, including the markers Glial Fibrillar Acid Protein and Neurofilament light chain. All the samples will be centrally measured in one of the participating centres at the end of the study. Patients will also be scanned before and after each period of treatment using a 3.0 T Magnet (GE Signa Architect). The baseline protocol will include the following sequences: 3DT1-weighted imaging, 3DT2-FLAIR, diffusion-weighted imaging, resting-state functional MRI and arterial spin labelling. Follow-up acquisitions will include resting-state functional MRI and arterial spin labelling. This protocol will provide information about changes in functional connectivity and cerebral perfusion associated with the different therapies. Baseline MRI would also be informative about potential characteristics associated with therapy response (eg, regional cortical thickness, white matter lesion load, structural and functional connectivity). Furthermore, blood biomarkers will provide information about potential neuroprotective effect and induction of neurogenesis of the studied therapies, which has been particularly suggested in animal models for TMS.[31 32]

Data management and analysis plan

The original protocols of the study will be stored in a locked office. Deidentified data will be saved on a secure electronic database. We will use Research Electronic Data Capture (REDCap) (Vanderbilt University), a secure, browser-based web application (http://project-redcap.org). Trial data, including scales and questionnaires, will be completed in paper form and then will be uploaded to REDcap.

Descriptive data will be shown as mean±SD or absolute frequency (percentage). Normality will be checked using the Shapiro-Wilk and Levene tests. Baseline and demographic characteristics will be presented.

The carry-over effect will be ruled out by comparing MFIS scores between visit 1 (before the first period) and visits 3, 5 and 7 (before the following periods and after washout periods) and using repeated measures analysis of variance. To evaluate the effect of treatments, we will use generalised mixed models. These models allow us to consider both the variability due to the patient and the effect of the interventions. Missing data will be described in terms of frequencies and percentages for each group and will be imputed using multiple imputation-chained equations. A p-value<0.05 will be used as the statistical threshold. The final analysis will be conducted according to the intent-to-treat principle.

We will also investigate the effect of sex, including this variable in the statistical models and evaluating the interaction with treatment response. Additionally, we will investigate baseline factors associated with treatment response. In this regard, we define 'responders' as those patients showing an improvement of 10 points in MFIS (total score).[20]

Cost analysis

All the resources and consumption (direct costs) and results associated with each alternative of treatment will be collected. A cost-effectiveness and cost-utility analysis will be modelled to estimate the incremental cost-effectiveness and cost-utility ration.

Data monitoring

The study will be monitored following the Good Clinical Practice standards and current legislation. An external company will perform monitoring. Regular visits and phone conversations with the monitor will be maintained according to the needs of the study. During visits, the monitor will review original patient data and documentation files and discuss any issues with the researcher and/or the study's sponsor. Protocol deviations identified will be notified to the principal investigator and sponsor. Severe protocol violations will be notified to the Spanish Agency of Medicines and Medical Devices (AEMPS) and Ethics Committee according to the current legislation.

Patient and public involvement

Patients were not involved in the development of the study protocol. Participants in the trial will be invited to provide feedback about the study and the procedures, and this feedback will be considered in future studies. The results of the trial will be presented in a newsletter sent to the participants and in specific meetings with patients.

Participation in the trial is voluntary, and patients will not receive any financial compensation.

ETHICS AND DISSEMINATION

Norms and laws of good clinical practices, biomedical research and clinical trials will be followed. The study has been approved by the Ethics Committee of the Hospital Clinico San Carlos and the AEMPS. All patients will sign the written informed consent before any study procedure. The study results will be presented at scientific conferences and published in peer-reviewed journals, regardless of the final results.

Author affiliations
[1]Department of Neurology, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISCC), Universidad Complutense de Madrid, Madrid, Spain
[2]Department of Psychology, University of Cadiz, Cadiz, Spain
[3]Institute of Research and Biomedical Innovation of Cadiz, Cadiz, Spain
[4]Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain
[5]Department of Neurology, Hospital Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[6]Department of Pharmacology and Toxicology, Universidad Complutense de Madrid, Madrid, Spain
[7]Unidad de Investigación Clínica y Ensayos Clínicos (UICEC), Instituto de Investigacion Sanitaria Hospital Clinico San Carlos, Madrid, Spain
[8]Department of Neurology, Hospital Universitario 12 de Octubre, Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED), Universidad Complutense, Madrid, Spain
[9]Department of Developmental Psychology and Education, Instituto Universitario de Neurociencia (IUNE), Universidad de La Laguna, La Laguna, Spain
[10]Department of Clinical Neurophysiology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

Twitter Jordi A Matias-Guiu @MatiasGuiu

Acknowledgements We acknowledge the collaboration of Laboratorios ERN, which manufactured amantadine and placebo. However, ERN did not have any role in the design of the study, data collection and will not participate in any phase of the trial including analysis, interpretation of the data and publication of the results.

Contributors JAM-G and JM-G drafted the manuscript. AP and NP-M have contributed to the drafted of specific sections in the manuscript. JAM-G, JG-R, MAH, MLM-G, AP, NP-M, JB-L, IP, JP and JM-G contributed to the conception and design of the study. All authors have contributed to the revision of the draft and have read and approved the final version.

Funding This research has been funded by the Instituto de Salud Carlos III through the project ICI20/00073 and cofunded by the European Union. This work is supported by Plataforma ISCIII de soporte para la Investigación Clínica of Hospital Clínico San Carlos, PT20/00017, funded by Instituto de Salud Carlos III and cofunded by the European Union. JAM-G is supported by Instituto de Salud Carlos III through project INT20/00079 (cofunded by the European Regional Development Fund 'A way to make Europe').

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Jorge Matias-Guiu http://orcid.org/0000-0001-8162-9043

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