Supplementary Appendix

Contents

Methods: Screening Visit Procedures

Screening visit procedures are outlined in the supplementary appendix. included a review of eligibility criteria, a physical and neurological examination, including EDSS, vital signs, blood work for assessing AST, ALT and GFR, and completion of the MFIS, Neuro-QoL fatigue item bank, ESS, and screening for depression (Hospital Anxiety and Depression Scale (HADS)-depression subscale). Participants were enrolled in the study and randomized to one of four medication administration sequence after the site study physician confirmed eligibility. The study drug of the first assigned period was handed out to the subject or mailed overnight after randomization.

Methods: Titration of Study Medications

During all treatment periods, participants started taking one red-colored capsule in the morning for one week. At week two, participants took one red-colored capsule and one blue-colored capsule in the morning. At the beginning of week three, participants took one red-colored and one blue-colored capsule in the morning and one red-colored capsule in the early afternoon. During week four and five, participants took one red-colored and one blue-colored capsule in the morning and in the early afternoon. During week six, participants tapered the study drug and took one red-colored and one blue-colored capsule in the morning. These instructions were provided to the participants, along with the medication bottles. The maximum dose of each medication taken during weeks four and five was 100 mg twice daily for amantadine, 100 mg twice daily for modafinil, and 10 mg twice daily for methylphenidate.

The above dosing schedule was followed by participants who could tolerate dose titration. The study nurse or medical personnel contacted each participant (via phone, email, or text message) at least five times during each treatment period to inquire about possible adverse events. Subjects who reported no side effects or tolerability problems were instructed to titrate the medication to the next planned dose. Participants who reported significant side effects or tolerability issues were instructed by study personnel, based on a planned algorithm (available in the study protocol), to either continue the current dose, reduce the dose or stop study medication depending on the severity of the side effects. If a participant did not answer the phone calls, emails, or text messages, it was assumed they had no side effects and could tolerate medication titration according to the instructions provided to them. Aside from weekly contact with participants through phone calls, emails, or text messages, there was no other measure of adherence to the study intervention.

Methods: Data collection

We used REDCap (Research Electronic Data Capture, http://project-redcap.org/)[1], a secure web application to build and manage online surveys, collect data, create the trial database, and access the data for analysis. Most of the trial data (including baseline values of MFIS and all questionnaires answered at the end of each study period) were directly captured via REDCap forms. Study coordinators, nurse, manager, and PIs periodically reviewed the data entry process to prevent data recording errors.

Methods: Sensitivity, exploratory, and heterogeneity of treatment effects analyses

In sensitivity analyses, carry-over effects were assessed by including an additional predictor of treatment in the previous time period (missing for time period 1) and testing its significance at 0.05.

In another sensitivity analysis, we analyzed the primary outcome of the study (MFIS total score) by evaluating the trial post hoc as a parallel-group trial and only using the outcomes obtained during the first treatment period. We used a linear regression model, adjusted for the baseline value of MFIS total score and study site for this analysis.

In post hoc exploratory analyses, we compared the proportion of patients who experienced at least 4-point or 10-point improvements in MFIS total score as compared to the baseline values. We used generalized estimating equations models, adjusted for treatment sequence, treatment period, and study site for these comparisons.

For each of the following potential effect modifiers measured at screening, a pre-planned analysis was performed to assess the heterogeneity of treatment effects.

1. Relapsing-remitting vs. progressive MS,
2. Depression (HADS: depression subscale score>11 vs. ≤11),
3. On disease-modifying treatments (yes vs. no),
4. Mild (EDSS <3.0) vs. more severe disability (EDSS≥3.0).

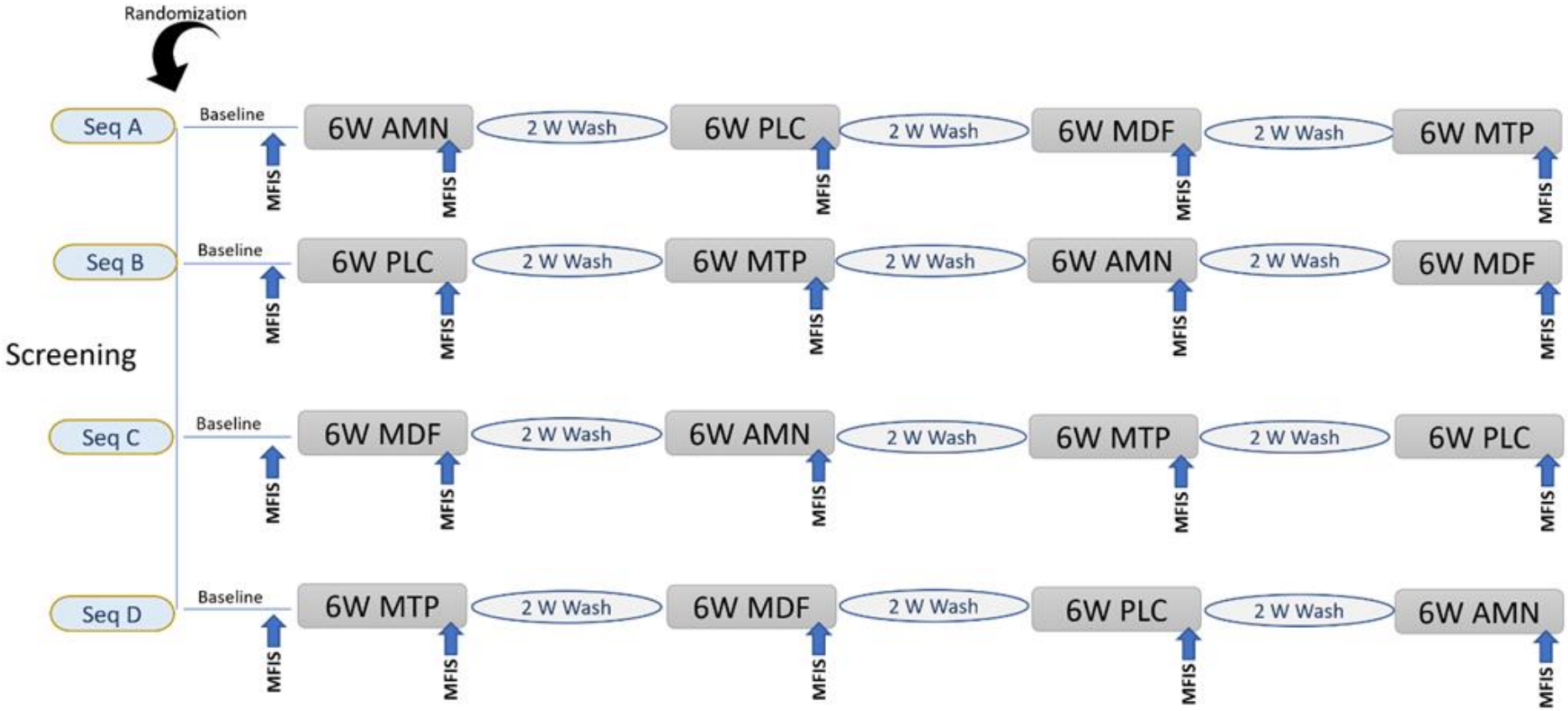
The primary mixed model analysis was repeated, including the interaction of the effect modifier with the treatment effects. If the p-value for interaction was 0.15 or less, subgroup analyses were to be conducted within each subgroup defined by the effect modifier. We also performed a similar post hoc analysis of heterogeneity of treatment effect according to the severity of the daytime sleepiness at baseline (analyzing the interaction between the baseline ESS score as a continuous variable and the treatment effect). We then performed a subgroup analysis based on the presence or absence of excessive daytime sleepiness (baseline ESS score>10 vs. baseline ESS score ≤10). This post hoc analysis was motivated by the report that the therapeutic effects of modafinil in MS fatigue could be modified by the severity of daytime sleepiness.[2]

Results: Post hoc analysis result

In post hoc exploratory analyses, there was no statistically significant difference in the proportion of participants whose MFIS total score improved on placebo compared to other study medications. The proportions of participants with at least a 4-point improvement in the MFIS total score compared to their baseline were as follows: 86 patients (70%) with placebo, 77 patients (62%)with amantadine, 94 patients (76%) with modafinil, and 95 patients (75%) with methylphenidate. The proportions of participants with at least 10-point improvement in the MFIS total score compared to their baseline were as follows: 62 patients (50%) with placebo, 56 patients (45%) with amantadine, 67 patients (54%) with modafinil, and 72 patients (57%) with methylphenidate.

In the post hoc exploratory analysis of the response to the question "Going forward, would you choose this medication as your fatigue treatment?", which was asked at the end of each medication period, the following proportions answered "yes": 39 patients (32%) with placebo, 41 patients (33%) with amantadine, 55 patients (44%) with modafinil and 55 patients (43%) with methylphenidate.

Figure S1. Study Design



AMN: amantadine, MDF: modafinil, MTP: methylphenidate, PLC: placebo, MFIS: Modified Fatigue Impact Scale, Seq: sequence, W: week, Wash: washout period

Figure S2. Titration Schedule of the Study Medications

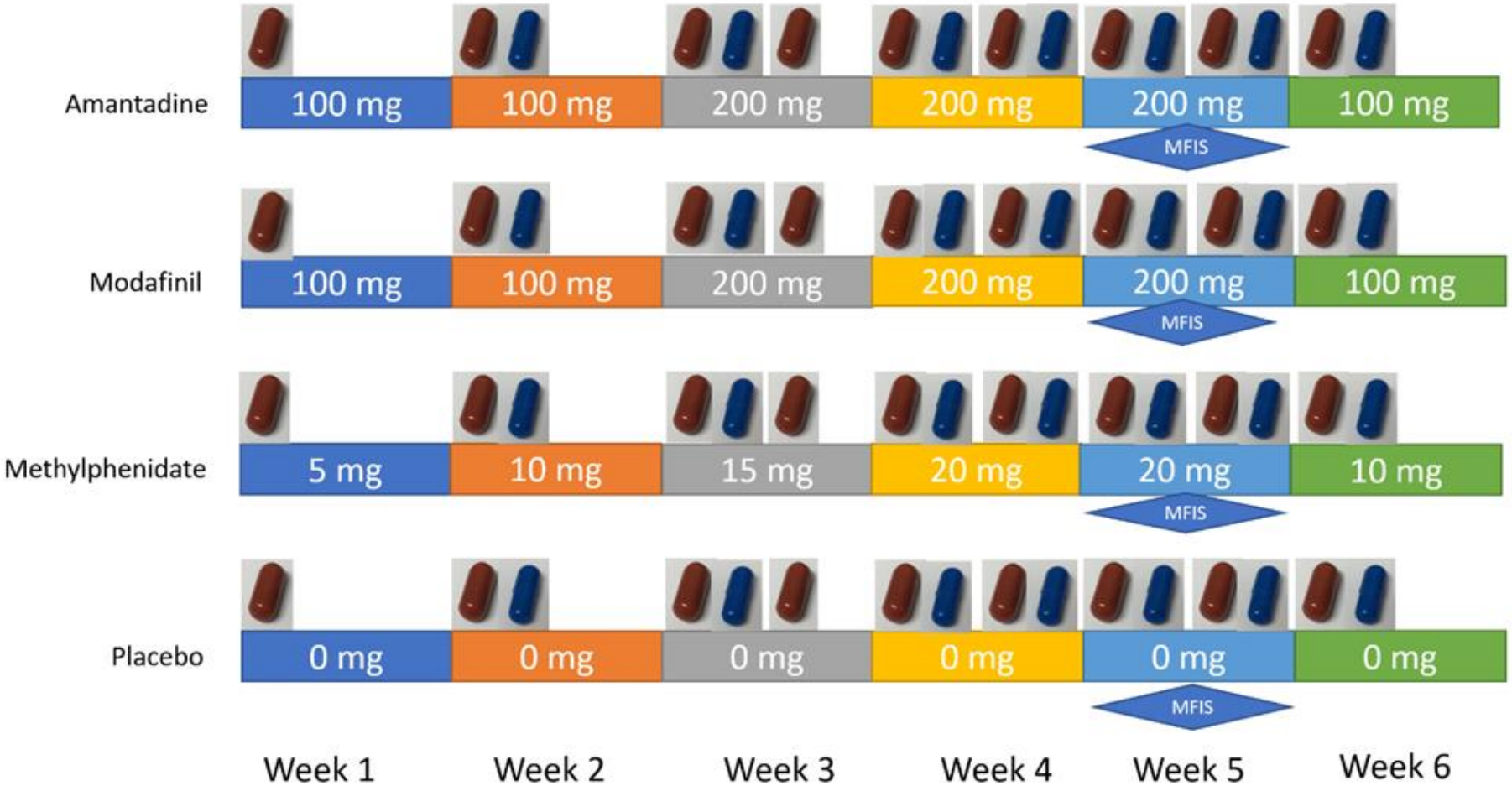
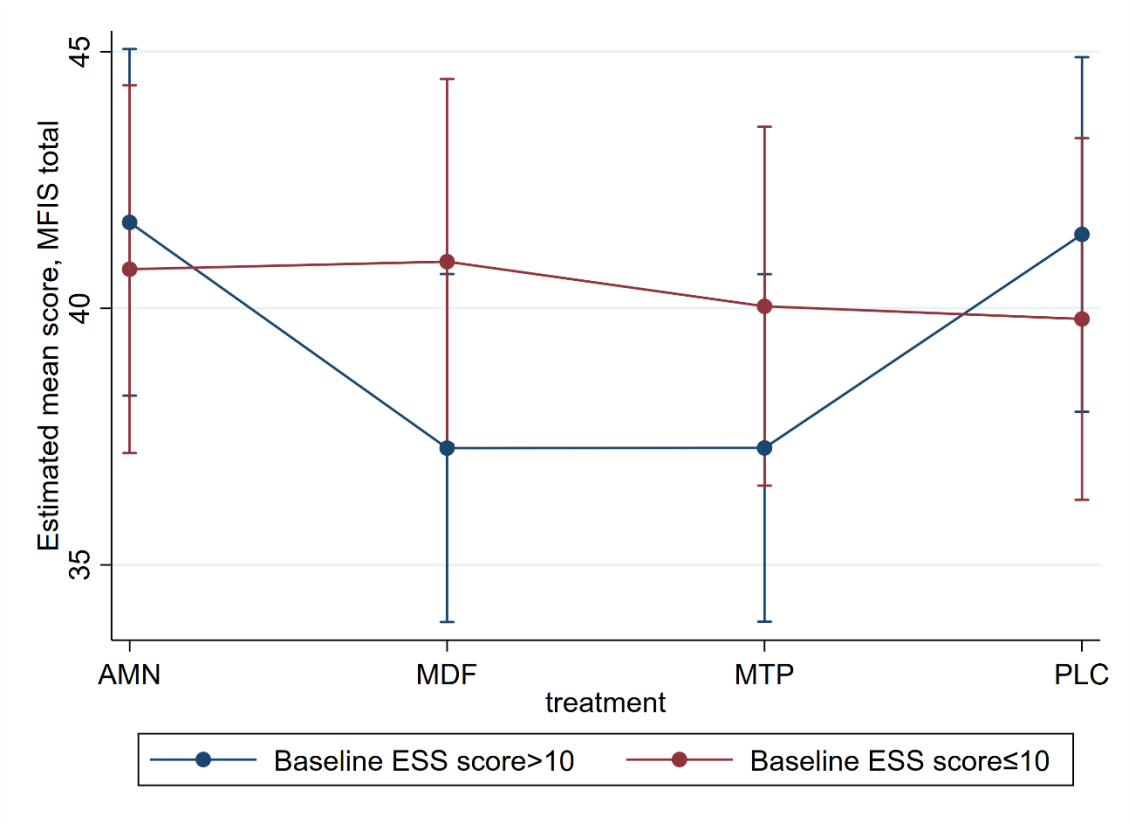


Figure S3. Interaction Between the Baseline ESS Score and Medication Treatment Effect on MFIS Total Score



ESS: Epworth Sleepiness Scale, MFIS: Modified Fatigue Impact Scale

Table S1. 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 apnea
History of long QT syndrome
History of atrial fibrillation or tachyarrhythmia (other than sinus tachycardia)
History of ischemic or hemorrhagic stroke
History of glaucoma
Tourette syndrome
History of severe untreated anemia (recent history of blood hemoglobin <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

Table S2. Baseline characteristics (at the time of screening) of participants who completed all four medication periods

	Total (N=111)
Age (Mean (SD))	47.3 (10.1)
Female	88 (79.3%)
Race	
White	84 (75.7%)
Black	19 (17.1%)
Other	8 (7.2%)
Ethnicity	
Hispanic	9 (8.1%)
MS subtype:	
Relapsing-remitting	84 (75.7%)
Secondary progressive	15 (13.5%)
Primary progressive	12 (10.8%)
Taking a DMT at the time of screening	91 (82%)
EDSS (Median (IQR))	3.0 (2.0-4.5)
HADS Depression-subscale score (Mean (SD))	5.7 (3.2)
MFIS Total score (Mean (SD))	53.6 (12.0)
MFIS Physical subscale Score (Mean (SD))	25.2 (5.9)
MFIS Cognitive subscale Score (Mean (SD))	23.4 (7.6)
MFIS Psychosocial subscale Score (Mean (SD))	5.0 (1.9)
ESS score (Mean (SD))	10.7 (5.2)
NeuroQol Fatigue Item Bank T-score (Mean (SD))	58.3 (6.0)

MS: multiple sclerosis, DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale, ESS: Epworth Sleepiness Scale, HADS: Hospital Anxiety and Depression Scale, MFIS: Modified Fatigue Impact Scale, NeuroQoL: Quality of Life in Neurological Disorders

Table S3. Pairwise Comparison of Estimated Means of MFIS Total Score Between Each Medication and Placebo

Medication	Medication	Estimate[$]	95% CI
MFIS Total Score			
Amantadine	Placebo	0.7	-2.2 to 3.5
Modafinil	Placebo	-1.6	-4.5 to 1.2
Methylphenidate	Placebo	-2.0	-4.8 to 0.8
MFIS Physical Subscale Score			
Amantadine	Placebo	0.5	-0.4 to 2.4
Modafinil	Placebo	-0.5	-1.9 to 0.9
Methylphenidate	Placebo	-0.9	-2.3 to 0.5
MFIS Cognitive Subscale Score			
Amantadine	Placebo	0.2	-1.2 to 1.5
Modafinil	Placebo	-0.8	-2.2 to 0.6
Methylphenidate	Placebo	-0.6	-2.0 to 0.7
MFIS Psychosocial Subscale Score			
Amantadine	Placebo	0.0	-0.4 to 0.3
Modafinil	Placebo	-0.3	-0.7 to 0.1
Methylphenidate	Placebo	-0.5	-0.8 to -0.1
NeuroQoL Fatigue T-score			
Amantadine	Placebo	-0.1	-1.6 to 1.3
Modafinil	Placebo	-0.6	-2.0 to 0.9
Methylphenidate	Placebo	-1.1	-2.6 to 0.3
ESS			
Amantadine	Placebo	0.6	-0.9 to 0.9
Modafinil	Placebo	-1.1	-2.0 to -0.2

Methylphenidate	Placebo	-0.5	-1.4 to 0.3

$ The estimated mean score of the first medication column minus the estimated mean score of placebo. Higher MFIS scores and NeuroQoL T-scores indicate worse fatigue. Higher ESS scores indicate worse daytime sleepiness. A positive estimate indicates favoring the placebo for fatigue or sleepiness reduction, while a negative estimate indicates favoring the medication.
MFIS total score range=0 – 84, MFIS physical subscale score range= 0 – 36, MFIS cognitive subscale score range= 0 – 40, MFIS physical psychosocial score range= 0 – 8, NeuroQoL average T-score for the population 50 and the SD=10, ESS score range= 0 – 24
ESS: Epworth Sleepiness Scale, MFIS: Modified Fatigue Impact Scale, NeuroQoL: Quality of Life in Neurological Disorders

Table S4. Pairwise Comparison of Estimated Means of MFIS Total Score Between Each Medication and Placebo in Participants With and Without Excessive Daytime Sleepiness

Medication	Medication	Estimate[$]	95% CI
Baseline ESS score>10			
Amantadine	Placebo	0.2	-3.6 to 4.0
Modafinil	Placebo	-4.1	-8.0 to -0.30
Methylphenidate	Placebo	-4.1	-7.9 to -0.2
Baseline ESS score≤10			
Amantadine	Placebo	0.7	-3.6 to 4.9
Modafinil	Placebo	1.0	-3.2 to 5.2
Methylphenidate	Placebo	0.3	-3.9 to 4.4

$ The estimated mean score of the first medication column minus the estimated mean score of placebo. Higher MFIS scores indicate worse fatigue. A positive estimate indicates favoring the placebo for fatigue reduction, while a negative estimate indicates favoring the medication.
MFIS total score range=0 – 84, ESS score range= 0 – 24
ESS: Epworth Sleepiness Scale, MFIS: Modified Fatigue Impact Scale

Table S5. Total number of adverse events in each period.

	Placebo	Amantadine	Modafinil	Methylphenidate
Period 1	29 [33]	50 [34]	53 [33]	46 [37]
Period 2	26 [32]	26 [32]	32 [34]	37 [31]
Period 3	8 [32]	12 [29]	34 [31]	24 [30]
Period 4	7 [27]	18 [32]	19 [27]	7 [31]

Data are the number of adverse events in each period [number of participants who took at least one dose of a study medication in that period].

References

1. REDCap [Internet]. [cited 2016 Jan 29];Available from: http://project-redcap.org/

2. Stankoff B, Waubant E, Confavreux C, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005;64(7):1139–43.