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Memantine for Fragile X-associated Tremor/Ataxia Syndrome (FXTAS): A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Objective—Memantine, an NMDA receptor uncompetitive antagonist, is currently approved by the Food and Drug Administration for the treatment of moderate to severe Alzheimer’s disease. Anecdotal reports have suggested that memantine may improve neurological and cognitive symptoms of individuals with the neurodegenerative disease, fragile X-associated tremor/ataxia syndrome (FXTAS); however, its efficacy and safety in this population have not been assessed in a controlled trial.

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Method—A randomized, double-blind, placebo-controlled, one-year trial in individuals with FXTAS ages 34–80 years. Primary outcome measures were the Behavioral Dyscontrol Scale (BDS) score and CATSYS intention tremor severity.

Results—Ninety-four participants were randomized from 205 screened; of those, 43 and 45 started memantine (titrated to 10 mg twice daily) and placebo, respectively. Thirty-four participants on memantine and 36 on placebo completed the one-year endpoint assessment (n=70). Intention-to-treat analysis showed that there was no improvement with respect to intention tremor severity (memantine vs. placebo: 1.05 ± 0.73 vs. 1.89 ± 2.19 , $p=0.047$) and BDS score (16.12 ± 5.43 vs. 15.72 ± 3.93 , $p=0.727$) at follow-up. Post hoc analyses of participants with early FXTAS (stage 3), late FXTAS (stage > 3) and different age groups (< 65 years and > 65 years) also indicated no significant improvement. More frequent mild adverse events (AEs) were observed in the placebo group, while more frequent moderate AEs occurred in the memantine group ($p=0.007$).

Conclusion—This randomized, double-blind, placebo-controlled trial of memantine for individuals with FXTAS showed no benefit with respect to the selected outcome measures compared to placebo.

Introduction

The fragile X mental retardation 1 (*FMRI*) gene premutation, with 55–200 CGG repeats, is present in about 1/130–260 females and 1/250–810 males in the general population.^{1,2} When premutation alleles are maternally transmitted, they may expand into the full mutation range, over 200 CGG repeats. The full mutation silences the gene, resulting in the absence or severe deficiency of the *FMRI* protein (FMRP), which manifests clinically as fragile X syndrome. Until recently, premutation carriers were believed to be unaffected with the exception of primary ovarian insufficiency, which can occur in up to 20% of female carriers.^{3,4} At the beginning of this millennium, neurological symptoms were first noted in aging premutation carriers and elevated levels of *FMRI* mRNA were found in premutation blood cells.^{5–7} These discoveries have shifted the paradigm and stimulated an exponential growth of research aimed at understanding the clinical and molecular features associated with the premutation.

Premutation carriers may have autoimmune, endocrine, neurological and psychiatric involvement.^{8–11} In late life, they may develop a neurodegenerative disease, fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS affects approximately 40% of male premutation carriers older than 50 years, up to 16% of female carriers, and has also been described in individuals with gray zone alleles (45–54 CGG repeats).^{12–15} Clinical manifestations include intention tremor, ataxia, parkinsonism, peripheral neuropathy, autonomic dysfunction, psychiatric symptoms and cognitive impairment.^{16–19} FXTAS diagnostic criteria have been proposed.^{7,20} Recently, Apartis et al¹⁹ called for a revision of these criteria. FXTAS progresses in six successive stages of physical disability outlined by Bacalman et al:²¹ 1) subtle or questionable tremor and/or balance problems; 2) minor tremor and/or balance problems, with minimal interference in activities of daily living (ADLs); 3) moderate tremor and/or balance problems with significant interference in ADLs; 4) severe tremor and/or balance problems, with need to use a cane or walker; 5) daily use of a

wheelchair; and 6) bedridden. Affected individuals may experience falls about six years after the onset of the motor signs; by 16 years into the course of the illness, half of the patients have significant difficulty with ADLs. Median survival is 21 years from the onset of the first signs of FXTAS.^{22,23}

Memantine is an uncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist. NMDA receptors act as calcium ion (Ca²⁺) channels which open when bound by glycine, glutamate, and/or NMDA.²⁴ Activation of the Ca²⁺ channels leads to an intracellular influx of Ca²⁺ and apoptosis.²⁵ NMDA antagonists decrease the permeability of the channel and prevent the influx of Ca²⁺, thus exerting a neuroprotective effect.^{24,26} NMDA antagonists have also been shown to attenuate NMDA-induced impairments in long-term potentiation, a central mechanism in learning and memory.^{27,28} Abnormal glutamate activity has been observed in mouse hippocampal premutation neurons with 170 CGG repeats grown in vitro, which have a reduced expression of vesicular GABA and glutamate transporters.²⁹

Memantine is currently approved by the Food and Drug Administration for the treatment of moderate to severe Alzheimer's disease (AD). A Cochrane database analysis found that memantine had a small beneficial effect at six months on cognition, behavior and the ability to perform ADLs in patients with moderate to severe AD.³⁰ Although there is insufficient evidence to support off-label indications, memantine has also been used for other cognitive disorders including mild AD, dementia with Lewy bodies (DLB), Parkinson's disease (PD) dementia and vascular dementia.^{24,30–33} Memantine may improve parkinsonism and dyskinesias in patients with PD, as well as neuropsychiatric symptoms in those with AD.^{34,35} Additionally, memantine has been explored as monotherapy or as an augmenting agent in anxiety disorders, bipolar disorder, opioid dependency, schizophrenia, traumatic brain injury and neuropathic pain, with mixed results.^{36,37} When used as add-on in refractory bipolar disorder, memantine has shown modest mood stabilizing properties and early antidepressant effects.^{37,38} In a year-long randomized controlled trial (RCT) of adults 40 years and older with Down's syndrome with or without dementia, there was no difference between memantine and placebo.³⁹ However a smaller RCT showed a moderate benefit on the California Verbal Learning Test (CVLT)-II Free Recall total score in adults ages 18–32 with Down's syndrome who took memantine for 16 weeks, compared to matched controls.⁴⁰

To date, one case report has illustrated improvement in both neurological and cognitive symptoms of FXTAS in a female carrier with memantine.⁴¹ We hypothesized that memantine improves the cognitive, neurological, and behavioral symptoms of FXTAS and tested this hypothesis with the first double-blind RCT conducted in individuals with FXTAS.

Methods

Study design and participants

The study protocol was approved by the Institutional Review Boards at the University of California (UC) Davis Medical Center and the University of Colorado School of Medicine. Participants were carriers with the premutation and gray zone alleles with FXTAS who were

enrolled in a large research study at the UC Davis Medical Investigation of Neurodevelopmental Disorders (MIND) Institute and the University of Colorado School of Medicine between September 2007 and August 2012. All participants gave informed consent. The inclusion criteria required that participants have definite, probable, or possible FXTAS in clinical stages 1–5. Exclusion criteria were: hypersensitivity to memantine, renal insufficiency, unwillingness to participate for a year, or current memantine treatment. Figure 1 represents the CONSORT diagram (<http://www.consort-statement.org/>) depicting participant flow through the RCT.

Randomization

Potential participants were self-referred or physician-referred to participate in studies of FXTAS. Participants were contacted by telephone or email; those who potentially met eligibility criteria were scheduled for a baseline visit. After investigators determined the FXTAS diagnosis and thus participant eligibility, randomization was done by the UC Davis pharmacy to either placebo or memantine. All study personnel, investigators and participants were blinded to the treatment assigned until completion of the trial.

Intervention

The study medication consisted of identical tablets containing either memantine or placebo provided by Forest Laboratories, Inc., at no cost to the investigators or participants. The study medication was either obtained at the UC Davis pharmacy after the baseline evaluation or shipped directly to the participants' home. The titration schedule was explained to participants; instructions were also included with the medication. Titration started with 5 mg (one tablet) once a day for one week, increasing to 5 mg twice a day for one week, then to 5 mg in the morning and 10 mg in the evening for one week and finally to 10 mg twice a day. The study coordinator called participants at 1 month, 3 months and 6 months to inquire whether they had experienced any adverse events (AEs).

Evaluation protocol

The baseline evaluation protocol consisted of genetic testing; a detailed medical history; a physical examination; a comprehensive neuropsychological test battery; the CATSYS protocol; and a psychiatric assessment, using a customized version of the Structured Clinical Interview for DSM-IV-TR (SCID)-I.^{42,43} The FXTAS diagnosis and stage were established by investigators, based on previously published criteria.^{7,20,21} The participants' complete medication lists were verified to exclude any possible interactions with memantine. Participants were asked to keep all other medications unchanged for the duration of the study. Hepatic and renal function tests were obtained and reviewed.

The neuropsychological test battery included the Wechsler Adult Intelligence Scale – Third edition (WAIS-III) at baseline, and the following measures, performed at baseline and one-year follow-up: the Mini Mental State Examination (MMSE); the Behavioral Dyscontrol Scale (BDS), which measures executive function, as detailed below; the CVLT, a word learning test; the Controlled Oral Word Association Test (COWAT), indicative of verbal fluency and considered a measure of executive functioning; and the Wechsler Memory Scale – Third Edition (WMS-III).^{44–49}

The Behavioral Dyscontrol Scale (BDS) is a 9-item, 27-point instrument which measures executive function, as the capacity for behavioral and attentional self-regulation.⁴⁶ The BDS has been widely used in studies of premutation carriers.^{50–52} CATSYS is a set of computer-assisted diagnostic instruments that can measure intention tremor, postural tremor, postural sway, manual coordination and reaction time.⁴² CATSYS has been previously used in premutation carriers.^{53,54} The SCID was customized prior to initiating this study to include the modules for mood, anxiety, substance use, somatoform and adjustment disorders and the screening questions for psychotic symptoms. Additionally, dementia and cognitive disorder not otherwise specified (NOS) were diagnosed through interview according to the DSM-IV TR criteria.⁵⁵

Participants returned one year later and were re-evaluated according to the same protocol, with the exception of WAIS-III and SCID, which were not repeated. The follow-up psychiatric evaluation was a one-hour interview, focused on life stressors and any subjective improvement or decline in participants' cognitive, emotional and functional status. The medical history and examination included medication review, side effects, and hepatic and renal function tests. After the follow-up assessment was completed, all participants were invited to exit the study and unblinded with regard to treatment status.

Molecular measures

Genomic DNA was isolated from peripheral blood leucocytes (5 ml of whole blood) using standard methods (Qiagen). Southern blot analysis, PCR analysis and calculation of the CGG repeat size were performed as described by Tassone et al.⁵⁶

Statistical analysis

The primary outcomes at one year follow-up were the BDS total score and CATSYS intention tremor severity. Thus, tests for primary efficacy were Bonferroni adjusted with a significance level of $p < 0.025$ (two-tailed) for $n = 70$ participants. Our *a priori* specified tests were t-tests and these are reported. Groups were also compared, adjusted for baseline measurements, using analysis of covariance (ANCOVA); the results remained the same. All other measures and associated analyses were secondary. AEs were summarized by severity, putative causal relation to drug, action taken to address the AE, and whether they required treatment. Student's t-test and Fisher's exact test were applied to continuous and categorical variables. All tests were at a level of 0.05, except for primary efficacy where the levels were 0.025. Analyses were implemented in SAS version 9.2 (SAS Institute, Cary, NC).

We aimed to detect a standardized effect size of 0.67 for 94 total participants (47 in each arm) at 90% power at level 0.025. We note that with 70 participants, the power is 80% to detect the same effect size.

Post hoc analysis

Post hoc analyses of younger participants (age ≤ 65 , $n = 33$), older participants (age > 65 , $n = 37$), those with early FXTAS (stage ≤ 3 , $n = 50$) and with late FXTAS (stage > 3 , $n = 20$) were also performed. For post hoc analyses, comparison for treatment effect was based on ANCOVA, adjusted for baseline measurement.

Results

Participant characteristics

Of the 205 participants assessed for eligibility, 94 were randomized into one of the two treatment arms. Randomized participants' demographic characteristics are shown in Table 1. There were no significant demographic differences between the memantine and placebo groups. Seventy participants completed the one-year follow-up, after excluding one participant who had experienced complete loss of physical functioning due to unknown etiology (see Figure 1).

Primary outcome analysis

The primary outcome measures were the BDS total score and CATSYS intention tremor severity. No treatment effects were found for BDS score: the memantine group mean was 16.12 (SD 5.43), compared to placebo group mean 15.72 (SD 3.93); $p=0.727$. Similarly, there was no treatment effect with respect to intention tremor, with the memantine group mean 1.05 (SD 0.73) and placebo group mean 1.89 (SD 2.19); $p=0.047$ (see Table 2).

Secondary outcome analysis

The secondary outcome measures included CATSYS postural and writing tremor severity and hand and finger tapping maximum frequency (indicating manual coordination). Secondary outcomes also included tests of declarative learning (CVLT), working memory (WMS-III working memory index score) and executive function (COWAT). Again, treatment effects were not observed with respect to any secondary measure (see Table 2).

Post hoc analyses

In post hoc analyses, we explored whether memantine was effective in subgroups that may potentially benefit from treatment. We considered subgroups of: (a) younger participants (age ≤ 65 years, $n=33$), (b) those with early FXTAS (stage ≤ 3 , $n=50$), (c) older participants (age > 65 years, $n=37$), and (d) those with late FXTAS (stage > 3 , $n=20$). No efficacy was found for post hoc analyses of primary or secondary outcome measures described above (results not shown).

Safety

There were 99 AEs reported for 48 participants (67.6%). Table 3 summarizes AE categories. There were no significant differences between memantine and placebo for causal relation to drug, action taken to address the AEs, and whether treatment was necessary. However, AE severity was significantly different between memantine and placebo: mild AEs were more frequent in the placebo group (55.81%) compared to memantine (25%) and moderate AEs occurred more often in the memantine group (41.07%) versus placebo (18.60%); $p=0.007$.

Additional considerations

We examined changes in psychotropic medications made during the study period that could have affected the participants' cognitive status. Participants were asked to keep all other medications unchanged while in the study however, in some cases, treating physicians made

adjustments based on the participants' clinical status. We examined changes in benzodiazepines, antidepressants and cholinesterase inhibitors (ChEIs) during the study period. See Table 4 for the detailed description of these medication changes.

Discussion

This is the first double-blind RCT in individuals with FXTAS. Memantine, an NMDA receptor antagonist, was selected due to its benefit on cognitive and behavioral symptoms of AD, off-label use for parkinsonism and several psychiatric disorders, and previous anecdotal reports of improvement of FXTAS symptoms in a female carrier. At one year, memantine showed no benefit over placebo on the primary outcome measures of intention tremor severity and executive function, and there were no significant differences on the secondary outcome motor and cognitive measures. Posthoc analyses in participants with early FXTAS (stage 3), late FXTAS (stage > 3) and different age groups (< 65 years and > 65 years) on the primary and secondary measures did not yield any differences either.

To date, memantine RCTs have been of variable durations, ranging from six weeks to one year, with a small benefit noted on cognition, behavior and ADLs at six months in AD.^{26,57,58} We chose one year as endpoint for the present study. FXTAS progresses over time; thus, one year was thought to be an adequate interval to measure outcomes, since shorter times could capture transient improvements. Due to the rigorous study design and inclusion/exclusion criteria, only 94 of the 205 carriers screened were randomized. Nevertheless, the final sample size (n=70) was sufficient to observe changes of a moderately large effect size with an 80% power. It should be noted that this study, similar to other clinical trials, does not rule out the possibility that some individuals with FXTAS may respond to memantine treatment.⁴¹

Memantine showed no benefit in a recent RCT in patients with frontotemporal lobar degeneration, highlighting its limited success in neurodegenerative diseases besides AD.⁵⁹ Similarly, there is insufficient evidence to date to recommend the use of memantine in PD dementia.³³ Even though dysfunction of the glutamate and GABA systems appears to play a role in the neurodegenerative changes of FXTAS, no single neurotransmitter has been clearly implicated.²⁹ The pathophysiologic mechanism in FXTAS is complex, involving elevated levels of *FMRI* mRNA, dysregulation and sequestration of intracellular proteins, altered miRNA processing, mitochondrial dysfunction and defective iron and zinc homeostasis.⁶⁰⁻⁶² Mitochondrial dysfunction is believed to be central to neurodegenerative processes and has recently been described in another triplet repeat disorder, Huntington's disease.^{63,64} Targeted treatments addressing the mitochondrial dysfunction, such as creatine and coenzyme Q10, have been studied in Parkinson's and Huntington's disease and might provide a good disease-modifying template for FXTAS.⁶⁵

In the present study, the CATSYS was used to measure tremor, postural sway and reaction time. The gold standard in assessment of motor parkinsonian features is the Unified Parkinson's Disease Rating Scale (UPDRS), which is widely used and has good reliability and validity.⁶⁶ CATSYS was selected as it had been previously used in premutation carriers; also, a recent study showed CATSYS measurements to be associated with clinician-rated

UPDRS items assessing tremor and bradykinesia.^{53,54,67} Future studies could include UPDRS in the protocol, to complement the CATSYS.

Psychiatric symptoms, in particular depression and anxiety, are common in premutation carriers.^{8,10,68} We examined changes in psychotropic medications during the study, in order to make sure these did not confound our results. For example, benzodiazepines may help mitigate tremor and anxiety, but have well known deleterious effects on cognition. By discontinuing benzodiazepines, the participants' cognition might have improved, however the severity of their tremor might have increased. Also, the titration of SSRIs or SNRIs might have improved cognitive functioning by ameliorating the deficits associated with anxiety and depression.^{69,70} However, in our study few medications were changed, with no differences across the two groups.

While targeted disease-modifying treatments for FXTAS are still awaiting development, symptomatic approaches have been used for its neurological, cognitive and psychiatric symptoms.^{17,71–73} The cholinesterase inhibitor donepezil has been used as a cognitive enhancer with good results in one case report.⁷⁴ Previous studies showed that adding memantine to ongoing donepezil treatment in patients with moderate to severe AD resulted in significantly better outcomes than placebo on measures of cognition, ADLs and behavior.⁷⁵ A similar rationale may inform future studies in FXTAS, using the memantine-donepezil combination. However the efficacy of ChEIs has not yet been established in this population; this step should be undertaken first, in order to avoid exposing patients to unnecessary side effects.

Conclusion

This was the first RCT in individuals with FXTAS; no significant benefit was observed for the cognitive enhancer memantine compared to placebo at one year. Limitations of this study included the moderate sample size, with fewer individuals in late FXTAS stages (n=20); using only the CATSYS to quantify tremor; and psychotropic medication changes, which are difficult to avoid in this population with multiple psychiatric comorbidities. Future studies exploring targeted treatments which address the molecular genetic aberrations, mitochondrial dysfunction and defective iron and zinc homeostasis are needed. In the meantime, symptomatic treatments will continue to offer partial comfort to patients with FXTAS.

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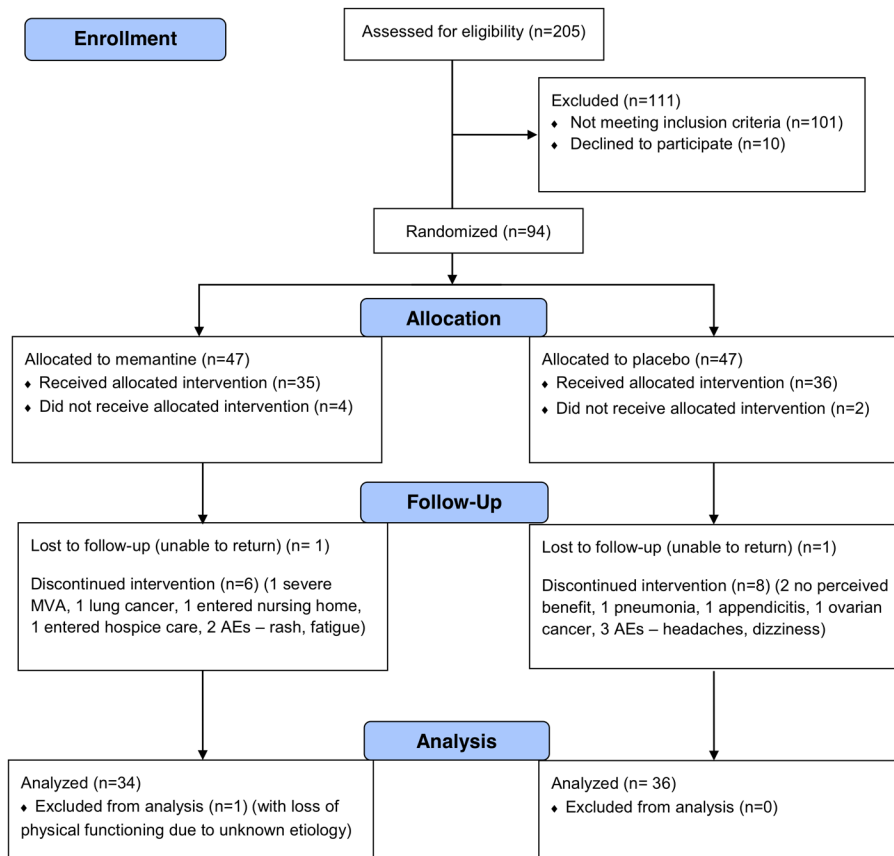
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Clinical Points

- Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disease which may occur in individuals with fragile X gene premutations. A dementia with prominent executive dysfunction may ensue in later FXTAS stages.
- Symptomatic treatments can address neurological and psychiatric aspects of FXTAS.
- This randomized, double-blind, placebo controlled clinical trial did not show benefit for memantine over placebo with regard to executive function and intention tremor in individuals with FXTAS.

Memantine Randomized Controlled Study CONSORT Flow Diagram



MVA = motor vehicle accident; AE = adverse events.

Figure 1.

Table 1

Demographic and clinical characteristics of the 94 randomized subjects.

Variable	Memantine			Placebo			P-value
	N	Mean	SD	N	Mean	SD	
Age (years)	46	64.70	9.70	47	66.30	7.00	0.339
Education (years)	47	15.28	2.85	47	15.28	2.90	1.000
CGG repeats	47	89	18	47	86	18	0.418
MMSE	32	29.03	1.09	36	28.81	1.83	0.535
	N	%		N	%		
Gender							
Female	15	31.91		19	40.43		0.519
Male	32	68.09		28	59.57		
Race							
White	47	100		47	100		
Ethnicity							
Hispanic	1	2.13		4	8.51		0.361
Non-Hispanic	46	97.87		43	91.49		
FXTAS diagnosis							
Possible	5	10.64		10	21.28		0.294
Probable	17	36.17		12	25.53		
Definite	25	53.19		25	53.19		
FXTAS stage							
1	1	2.13		3	6.38		0.653
2	16	34.04		11	23.40		
3	16	34.04		19	40.43		
4	12	25.53		13	27.66		
5	2	4.26		1	2.13		
Cognitive diagnosis^a							
Cognitive d/o NOS	3	6.36		4	8.51		
Dementia	4	8.51		4	8.51		

^aBased on DSM-IV-TR criteria

Cognitive d/o. NOS = cognitive disorder not otherwise specified; MMSE = Mini Mental State Examination; SD = standard deviation.

Table 2

Primary and secondary outcome analysis.

	Memantine						Placebo						P-value*
	Baseline			Follow-up			Baseline			Follow-up			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Primary outcomes													
BDS total score	34	17.44	5.19	34	16.12	5.43	35	15.66	4.11	36	15.72	3.93	0.727
Intention tremor ^a	32	1.31	1.02	32	1.05	0.73	35	1.77	1.78	32	1.89	2.19	0.047
Secondary outcomes													
Postural tremor ^a	31	0.23	0.24	31	0.20	0.23	35	0.57	0.96	32	0.77	1.94	0.109
Writing tremor ^a	32	0.51	0.64	32	0.37	0.49	35	0.72	1.10	32	0.72	1.02	0.087
Hand tapping ^b	29	5.52	1.68	25	5.50	1.54	30	5.63	1.30	25	4.72	1.74	0.098
Finger tapping ^b	26	6.16	1.60	25	5.68	1.55	29	6.17	1.82	23	5.92	1.68	0.606
CVLT ^c	32	42.22	9.52	33	45.61	12.84	36	42.72	11.50	36	43.22	13.31	0.453
COWAT ^d	34	40.88	17.23	33	38.12	14.36	36	33.61	14.16	36	35.78	16.08	0.527
Working memory score (WMS-III)	31	103.81	15.37	29	106.17	17.42	31	99.87	13.14	31	99.68	13.21	0.108

* Significance at level 0.025 for primary outcomes (BDS score and intention tremor severity) and 0.05 for secondary outcomes

^a Intention, postural and writing tremor severity in dominant hand, measured with CATSYS (m/s²)

^b Hand and finger tapping maximum frequency in dominant hand, measured with CATSYS (Hz)

^c List A 1–5 trials score

^d F+A+S score

BDS = Behavioral Dyscontrol Scale; CVLT = California Verbal Learning Test; COWAT = Controlled Oral Word Association Test; SD = standard deviation; WMS = Wechsler Memory Scale.

Table 3

Adverse events.

	Memantine		Placebo		P-value*
	N	%	N	%	
Drug related					0.381
Not related	22	39.29	24	55.81	
Not likely	12	21.43	7	16.28	
Possible	18	32.14	11	25.58	
Probable	4	7.14	1	2.33	
Severity					0.007
Mild	14	25.00	24	55.81	
Moderate	23	41.07	8	18.60	
Severe	18	32.14	11	25.58	
Very severe	1	1.79	0	0	
Action taken					0.077
Dose reduced	4	7.14	0	0	
Drug discontinued	4	7.14	7	16.28	
None	48	85.71	36	83.72	
Treatment required					0.687
No	30	53.57	25	58.14	
Yes	26	46.43	18	41.86	

* Fisher's exact test

N = number of adverse events (AE); Individuals may have experienced more than one AE.

Table 4

Psychotropic medication changes in the 70 participants who completed the trial.

Class	Group	Changes
BZD	Memantine (n=4)	None
	Placebo (n=5)	None
ChEI	Memantine (n=1)	1 switch within class (rivastigmine patch to oral donepezil)
	Placebo (n=3)	None
SSRI	Memantine (n=6)	3 started new medication; 1 dose increase; 1 dose reduction; 1 switch outside of class (sertraline to bupropion)
	Placebo (n=10)	1 started new medication; 4 dose increase
SNRI	Memantine (n=5)	1 switch within class (venlafaxine to duloxetine)
	Placebo (n=2)	None
Other *	Memantine (n=6)	None
	Placebo (n=5)	1 switch from olanzapine to aripiprazole

BZD = benzodiazepine; ChEI = cholinesterase inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor.

* Includes: amitriptyline, aripiprazole, bupropion, gabapentin, lamotrigine, methylphenidate, mirtazapine, modafinil, olanzapine, pramipexole, quetiapine, risperidone, topiramate.