Memantine (Namenda®) for non-motor features of Parkinson's disease: A double blind placebo controlled trial

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ABSTRACT

Background: Memantine is currently approved for the treatment of moderate to severe Alzheimer's disease, but has long been used to treat fatigue, apathy, depression, and other related conditions.
Methods: We conducted a single center, double-blind placebo controlled trial of memantine, titrated to 20 mg/day, in PD patients. Inclusion criteria were intentionally broad and included both fluctuating and non-fluctuating patients with a UPDRS "motivation" (#4) score of greater or equal to 2. Patients with dementia or on amantadine were excluded. After baseline assessments, patients (N=40) were randomized to drug and placebo groups. They received a battery of neuropsychiatric assessments. After a safety call (2 weeks after baseline) they returned for identical assessments at week 8. An 8-week open label extension was started if desired.
Results: Patient demographics (age 69.1±7.8; 24 males), were similar in the drug and placebo groups. Four dropped while on drug vs. none on placebo. Two of 36 dropped out over the 8 week open label section. Of the 34 who completed the final open label visit, 24 elected to stay on memantine after the study. However, there was no change in UPDRS section I or II, Epworth sleepiness scale, fatigue severity scale, Hamilton depression scale, or Conner adult inventory. UPDRS "on" motor scores tended to improved, p=0.019.
Discussion: Memantine was well tolerated in PD and tended to improve motor scores; however, specific measures of sleepiness, fatigue, depression, and attention did not improve. The majority of subjects elected to stay on the drug after the open label extension suggesting some unassessed benefit.

INTRODUCTION

Memantine is currently approved for the treatment of moderate to severe Alzheimer's disease, but has long been used to treat fatigue, apathy, depression, and other related conditions in several disease states. 1-6 The drug has been used safely in PD and reported to improve cardinal motor features and cognition, although not dyskinesia. 7-10 It may also improve chorea in Huntington's disease. 11, 12 The mechanism is not entirely established but the drug seems to stabilize glutaminergic tone. It is an uncompetitive, low-affinity, open-channel blocker that enters the N-methyl-D-aspartate (NMDA)-type glutamate receptor preferentially when it is excessively open and has a relatively "fast off" so that it does not substantially accumulate in the channel to interfere with normal glutamate transmission. 13 The drug may also block nicotinic acetylcholine receptors. 14

Anecdotally, we have heard a wide variety of positive outcomes from PD patients taking this drug. These include such things as more energy, better mood, improved sense of humor, and most commonly "more like his old self". Based on these testimonials we conducted an exploratory placebo controlled study to evaluate a broad scope of predominately non-motor problems seen in PD.

METHODS

We conducted a single center, double-blind placebo controlled trial of memantine in 40 PD patients. Patients were enrolled over 11 months from the Parkinson Disease Center and Movement Disorder Clinic at Baylor College of Medicine. PD was diagnosed using standard criteria. Specific inclusion criteria were intentionally broad and included both fluctuating and non-fluctuating patients with a UPDRS "motivation" (#4) score of greater or equal to 2. Patients with dementia (MMSE<24) or taking amantadine were excluded.

The patients signed an informed consent approved by the Baylor College of Medicine Institutional Review Board and the study was registered on Clinical Trials.gov #NCT00646204. The study was funded by a grant from the Forest Research Institute.

After baseline assessments, patients (N=40) were randomized equally to drug (N=20) and placebo (N=20) groups. This was done by a computerized random number generator by a coordinator not otherwise involved in the study. Patients completed medical and medication histories, a Unified Parkinson's Disease Rating Scale (UPDRS), a battery of neuropsychiatric assessments (see Table 2), global impressions, and adverse events. Patients were not allowed to change other PD medications. The drug/placebo dosing began at 5 mg/day and increased to 5 mg 2x/day, 10 mg / 5 mg, and finally 10 mg 2x/day, in weekly increments. After a safety call (2 weeks after initiation) they returned for identical assessments at week 8. Drug accountability was documented at each visit. An 8-week open label extension was started if desired using the same protocol and assessments.

Tabulations and univariate statistics on difference scores between visits were run using Intercooled Stata V8.0 for windows (Stata Corporation, College Station, Texas 77845), and included Student's t-test with equal variances and contingency table analysis using Pearson's Chi-square test. Statistics were done using LOCF. Corrections for multiple comparisons were not done.

RESULTS

Thirty-six of 40 completed the 8-week placebo controlled trial. All 4 patients who dropped were in the drug group. Three were for adverse events: shoulder pain (1), lethargy (1), dyskinesia (1), and one sited no specific reason. The two open patients dropped for adverse events: nausea/confusion/sleepiness (1), and anxiety (1). Two of those 36 who entered the 8 week open label portion withdrew consent . Of the original 40, 24 continued on drug after completion of the study.

Randomization resulted in no demographic differences between groups. [Table 1] Moderate/marked improvement was reported by 1/20 on placebo and 4/16 on drug. Mild improvement was reported by 3/20 on placebo and 2/16 on drug. There were no significant differences in any of the neuropsychiatric assessments, although most tended to favor memantine. [Table 2]

Adverse events were generally mild. During the placebo controlled phase adverse events on drug included sedation (2), confusion (1), pain (1), obsessive thinking (1), lethargy (1), jerky movements/dyskinesia (1). Adverse events on placebo included nausea (3), dizziness (2), nervousness (1), hypertension (1), limb numbness (1), anxiety (1), weight loss (1), jerking (1).

Table 1

	Memantine (N=20)	Placebo (N=20)	All (N=40)
Sex	8 F, 12 M	8 F, 12 M	16 F, 24 M
Age	69.2(7.9)	68.9 (8.4)	69.1 (7.2)
"Off" H & Y	1.5 1 2 4 2.5 10 3 4 4 1	1.5 0 2 11 2.5 5 3 4 4 0	1.5 1 2 15 2.5 15 3 8 4 1
L-dopa dose#	519 (351)	539 (306)	528 (327)
Fluctuating	12	11	23
MMSE	27.7 (1.0)	28.7 (1.5)	28.1 (1.8)
Common Co-morbidities	Depression 6 Anxiety 2 Hypertension 8 Cholesterol 3 Arthritic 4 GI 4 Thyroid 2	Depression 10 Anxiety 4 Hypertension 10 Cholesterol 6 Arthritic 5 GI 5 Thyroid 2	Depression 16 Anxiety 6 Hypertension 18 Cholesterol 9 Arthritic 9 GI 9 Thyroid 4

(L-dopa + L-dopa CR*.75 + pergoline*100 + pramipexole*100 + ropinirole*33)*1.1 if on COMT inhibitor

Table 2

	Baseline Placebo	Final Placebo	Baseline Memantine	Final Memantine	P, change in placebo vs. drug	Absolute change placebo vs. drug	Final Open Label
UPDRS "on" ADL	12.0(4.1)	11.9(4.7)	13.8(6.0)	13.8(6.3)	NS	0.1#	12.2 (5.2)
UPDRS "on" motor	19.0(10.5)	19.7(11.8)	24.3(14.3)	22.7(14.6)	0.19	2.3*	19.1 (12.3)
Conner Adult	21.8(12.8)	17.5(12.5)	25.3(14.8)	20.7(13.5)	NS	0.3*	21.7(13.3)
Hamilton-Depression	10.1(5.0)	8.1(3.7)	10.7(5.0)	8.9(5.5)	NS	0.6*	8.8(5.1)
Fatigue Severity scale	37.2(14.3)	35.7(16.9)	37.6(14.2)	37.4(17.7)	NS	1.3#	34.2(16.1)
Epworth Sleepiness Scale	10.1(6.5)	10.4(5.4)	12.9(5.8)	11.9(6.2)	NS	1.2*	10.1(5.3)
PDQ 39	43.7 (25.3)	41.1 (29.0)	56.1 (30.5)	53.1 (33.3)	NS	0.3*	46.8 (29.9)
Health V.A.S.	70.0 (12.7)	68.3 (17.4)	69.6 (16.7)	65.4 (21.6)	NS	2.5*	64.3 (20.4)

DISCUSSION

Memantine was generally well tolerated in patients with PD and more than half of those who started the drug elected to continue it after the study. There was a trend to improve "on" motor scores, which would have been significant but for one outlier who worsened by 13 points. However, we were not able to demonstrate superiority over placebo on a set of standardized assessments commonly used to evaluate non-motor features in PD including fatigue, attention, sedation, and depression. There are several possible explanations. First, this was a pilot study not powered to detect modest change in scales. Second, the scales may not be appropriate or sensitive enough to the beneficial effects of this medication in this population. Anecdotally, patients often report "feeling better" without more specific explanations. Nevertheless, this study does not support initiating larger studies, at least with these endpoints.

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