

# A double-blind, placebo-controlled trial of memantine in age-associated memory impairment (memantine in AAMI)

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## SUMMARY

**Objectives** To determine the safety and efficacy of memantine in treating Age-Associated Memory Impairment (AAMI).

**Methods** Sixty adults between 50–79 years of age meeting diagnostic requirements for AAMI were randomly assigned to either memantine (titrated to 20 mg) or a matched placebo and treated for 90 days. An extensive battery of computerized cognitive tests was administered at screening, baseline and, thereafter, at monthly intervals.

**Results and Conclusion** Study results suggest that the primary cognitive effects of memantine in this population are on attention and information processing speed, rather than on memory. There were no differences in adverse events between memantine and placebo. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS—memantine; Age-Associated Memory Impairment; memory; attention; aging; cognition

## INTRODUCTION

Memantine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that has been shown in at least six large, controlled clinical trials to be of therapeutic value in moderate to severe Alzheimer's disease (AD; e.g. Winblad and Portis, 1999; Reisberg *et al.*, 2003; Tariot *et al.*, 2004; Reisberg *et al.*, 2006). In AD it is thought to act by decreasing excess calcium influx during activity of glutamatergic neurons (Rogawski and Wenk, 2003). On the basis of these studies, the drug has been approved for the treatment of moderate to severe AD in Europe and the United States (see Ferris, 2003; McShane and Schneider, 2005 for reviews).

The intent of this pilot study was to determine whether memantine has the potential to improve learning, memory or attention in subjects with Age-Associated Memory Impairment (AAMI; Crook *et al.*, 1986). AAMI describes healthy people over 50 years of age who have experienced cognitive losses since early adult life that lie within the bounds of normality. Criteria for AAMI include both subjective and objective evidence that memory loss has occurred since early adult life in the absence of disease or trauma of possible etiologic significance. People with AAMI are not at significantly greater risk for developing AD as compared to risk in the total elderly population (Youngjohn and Crook, 1993).

Memantine was considered a logical candidate for study in AAMI because glutamate has been argued to play the same role in AAMI as in AD (McEntee and Crook, 1993) and, in contrast to the cholinesterase inhibitors, adverse effects have been minimal in the studies cited above.

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## METHODS

### *Subjects*

Subjects eligible for inclusion were men or women between 50–79 years of age who complained that they have experienced memory loss over the course of adult life (Crook *et al.*, 1992) and performed at least one SD below the mean for *young* adults on a standardized memory test (Wechsler, 1988). Prospective subjects were excluded from the sample if they scored 26 or less on the Mini-Mental State Examination (Folstein *et al.*, 1975) or showed other evidence of dementia (McKhann *et al.*, 1984); showed evidence of depression as reflected by a score of 11 or higher on the 30 item Geriatric Depression Scale (GDS; Yesavage *et al.*, 1983); or showed evidence on history or examination of medical or neurologic problems that could account for memory loss over the course of decades. Subjects were also excluded if they were taking, or were likely to require over the course of the study, a wide range of drugs that can impair cognition. These were the criteria for AAMI originally described in greater detail by Crook *et al.* (1986).

### *Study design*

This was a fully randomized, double-blind, placebo-controlled, parallel-groups study. All subjects read and signed an informed consent document prior to screening.

The study entailed a screening visit, assessment of inclusion and exclusion criteria, followed by randomization to treatment for those subjects who met study criteria. Subjects were seen in the clinic for baseline evaluation on all tests that served as outcome measures, provided with a supply of either memantine or identically-appearing placebo and scheduled for a follow-up visit 1 month later. Memantine or placebo was supplied in titration packets and dosage was increased from 10 mg (5 mg b.i.d.) to 20 mg (10 mg b.i.d.) daily over a 1-month period. Thereafter dosage was maintained at 20 mg for the duration of the study. Compliance was assessed through pill counts. Subjects were seen in the clinic for testing and assessment of any adverse events (through spontaneous report) on three occasions, at monthly intervals during the 3-month period of the study.

### *Outcome measures*

The outcome measures used in the study consisted of a standard neuropsychological test of learning and memory (Rey Auditory Verbal Learning Test, RAVLT;

Rey, 1961), and two computer-administered batteries: (1) the Psychologix Computerized Cognitive Test Battery focusing on learning and both immediate and delayed recall of visual and verbal information (Larrabee and Crook, 1991) and (2) the CogScreen Test Battery focusing on attentional processes (Kay, 1995; Birkmayer, *et al.*, 2002). Both test batteries are widely used in clinical trials and academic, military and industrial research. Descriptions of tests employed in this study from the two computerized batteries are provided in Table 1.

The RAVLT (Rey, 1961) consists of 15 nouns read aloud for five consecutive trials, followed by an interference trial, which is then followed by a free recall test of the initial 15 nouns. After a 30-min delay period, the subject is again required to recall the initial set of nouns. Thus, there is an immediate and a delayed-recall score.

### *Statistical analysis*

Change from baseline to the final evaluation, after 3 months of treatment, was analyzed on each outcome measure using analysis of covariance procedures, with the baseline score as the covariate. The treatment groups were also compared on each outcome measure after 1 and 2 months of treatment. Treatment groups were also compared on adverse events that emerged during the course of the study.

Only subjects who completed at least one post-dosing assessment and received at least one dose of study medication were included in the analysis. As specified in the data analysis plan, tests of significance were one-tailed, testing the hypothesis that memantine is of therapeutic value.

Sample size was calculated using the most age-sensitive test administered as an outcome measure, the SDCIRACC from the Cogscreen Battery. With that test, sample size of 30 patients per treatment group provides power of 80% to find a statistically significant treatment effect. This corresponds to a mean difference between groups of 0.6 SD.

## RESULTS

### *Demographics and clinical characteristics*

Thirty subjects were entered into each treatment group as planned. As shown in Table 2, the groups were quite similar with regard to age, gender, and racial distributions, as well as body size. In no case were differences between the treatment groups statistically significant. Subjects in both groups showed no signs of depression (GDS) or dementia (MMSE) at screening

Table 1. Descriptions of tests in the Psychologix and Cogscreen Test Batteries

*Psychologix Battery of Learning and Memory Tests* (Crook, 1993)

*Name-Face Association Test (NFA)—Immediate and Delayed Recall*—In this test, subjects are presented with a live video presentation of individuals introducing themselves by common first names. After a series of introductions, recall is assessed by showing the same individuals in a different order and asking the subject to provide the name of each person. There are two learning trials in which fourteen name-face pairs are presented and recall is assessed. Delayed recall is assessed 30 min later.

*Facial Recognition Test—Delayed Non-Matching to Sample (DNM)*—On the first trial of this test, subjects are presented with a single facial photograph on a touch screen monitor and asked to touch the face. On each of 24 subsequent trials, a new face is added to the array and the subject is required to identify the new face by touching it in the monitor. Each trial is separated from the preceding trial by an eight second interval during which the screen is black. Feedback is provided on each trial in the form of a red square that appears momentarily around the photograph if it is correctly identified.

*First-Last Names Test (FLN)—Immediate and Delayed Recall*—In this test subjects are presented on the computer screen with six pairs of first and last names and asked to read each pair aloud. One pair is presented at a time. The last name corresponding in each pair is then presented and subjects are asked to provide the corresponding first name. This procedure is repeated three times with the same name pairs and then delayed recall is assessed after a 30 min delay.

*Telephone Dialing Test (TDT)*—This task is a variation on the standard digit recall paradigm. Participants are presented with a series of ten-digit (long distance) telephone numbers on the monitor screen and asked to read them aloud. The number then disappears from the screen and subjects are instructed to dial the number on a representation of a touch-tone phone on the computer screen. On two of these trials the subject encounters 'interference' in the form of a busy signal and must redial from memory. Four trials are conducted, with credit being given for each digit dialed in the correct position, regardless of errors made elsewhere in the sequence.

*Cogscreen Attention and Concentration Battery* (Kay, 1995)

*Symbol Digit Coding (SDC)*—SDC is a computer analogue of the conventional symbol-substitution task found in the WAIS-R Digit Symbol subtest and the Symbol Digit Modalities Test. Six symbol-digit pairs are displayed continuously throughout the test near the top of the screen. The participant is instructed to remember the symbol-digit pairs for a subsequent memory test. In the center of the screen, a line of symbols in random order is presented with blank spaces directly beneath each symbol. The subject selects the associated digit for each symbol. As each row is completed, a new row appears. Performance measures include response speed (SDC Speed; SDCRTC), response accuracy (SDC Accuracy; SDCACC) the number of items completed correctly per minute (SDC Thruput; SDCPUT). This subtest measures attention, visual scanning, working memory, and speed of information processing.

*SDC Immediate Recall Task*—This task immediately follows the 90-sec trial of the SDC task. Six symbols are presented in random order. The subject's task is to recall the corresponding digits. A measure of recall accuracy (SDC Immediate Recall Accuracy; SDCIRACC) is the only score for this task. This task provides a measure of short-term visual paired-associate memory.

*SDC Delayed Recall Task*—SDC Delayed Recall Task presents a 20-min delayed recall trial of the symbol-digit pairs. A measure of recall accuracy (SDC Delayed Recall Accuracy; SDCDRACC) is the only score for this task. This task provides a measure of delayed recall from visual paired-associate memory.

*Visual Sequence Comparison (VSC)*—VSC simultaneously presents the respondent with two alphanumeric strings, one on the right and the other on the left half of the screen. The respondent selects [SAME] or [DIFFERENT] for each pair, indicating whether the same characters are presented in the same order for both sequences. The strings vary in length from four to eight items. For each pair, the strings may differ by one or two items. Half of the 20 sequence pairs present the same sequence, and half present a different sequence. Performance measures include the speed (VSC Speed; VSCRTC) and accuracy (VSC Accuracy; VSCACC) of responses, and the number of problems correctly completed per minute (VSC Thruput; VSCPUT). Mental functions addressed by this test include visual attention, working memory, verbal-sequential processing, and visual-perceptual speed.

*Divided Attention Test (DAT)—Indicator Alone Task.* For the DAT Indicator Alone task, the respondent watches a cursor move vertically within a circle that is divided into central, upper, and lower sections. When the cursor crosses into the upper or lower sections, the respondent's task is to press a box marked 'CENTER' with the touchscreen stylus. DAT Indicator Alone Speed (DATIRTC) is the median amount of time the indicator spends in the upper and lower section of the circle prior to being centered by the respondent. DAT Indicator Alone Premature Responses (DATIPRE) represents number of premature centering responses. Premature responses are indicated if the respondent presses the 'CENTER' key before the cursor moves into the upper or lower sections.

and were similar in complaining of memory decline (MAC-Q and MAC-S). There was also no statistically significant difference between treatment groups at baseline on the RAVLT, a standard neuropsychological test of memory.

*Efficacy*

In efficacy analyses we examined both Intent-To-Treat ('ITT,'  $n = 60$ ) and Compliance with Protocol (CP;  $n = 54$ ) cohorts. We did not impute scores in the ITT

Table 2. Demographic and Clinical Characteristics of Study Subjects

Characteristic	Memantine	Placebo
	Mean (SD)	Mean (SD)
Sample size	30	30
Gender (% female)	60%	70%
Race (% Caucasian)	93%	87%
Age	65.9 (7.6)	67.5 (9.6)
Body weight (pounds)	178 (42)	176 (39)
Height (inches)	66 (5.1)	65 (4.7)
Geriatric Depression Scale	4.8 (3.0)	5.8 (3.2)
MMSE	28.9 (1.1)	28.6 (1.1)
MAC-S	29.3 (6.8)	33.8 (8.1)
RAVLT, free recall, 30 min total delay	7.1 (2.8)	7.8 (3.6)

analyses so there was no difference between the two cohorts at the conclusion of treatment. In the following Tables and Figures we report analyses from the CP cohort, showing one-tailed *t*-tests. Results were very similar for the ITT analyses.

### Standard neuropsychological outcome measure

Figure 1 illustrates changes in the two treatment groups over the course of treatment on the standard neuropsychological memory test included in the study, the Rey Auditory Verbal Learning Test (RAVLT). Figure 1 shows the mean response and 95% confidence intervals for the immediate and 30-min delayed results for both drugs after 1, 2, and 3 months of treatment. There were no statistically significant group differences or trends on either immediate or delayed recall at any point.

### Psychologix computerized test battery

As shown in Figure 2, there were no significant group differences or trends on any of the learning and memory tests in the Psychologix test battery. The two graphs on the left side of Figure 2 show the mean response and 95% confidence intervals for the immediate and 30-min delayed recall results. The graphs on the right side of Figure 2 show the results after 1, 2, and 3 months of treatment. There was also

## RAVLT Results at One, Two, and Three Months

Graphs show adjusted mean response and 95% confidence intervals for each drug group.

### Adjusted Mean RAVLT Scores with 95% Confidence Intervals

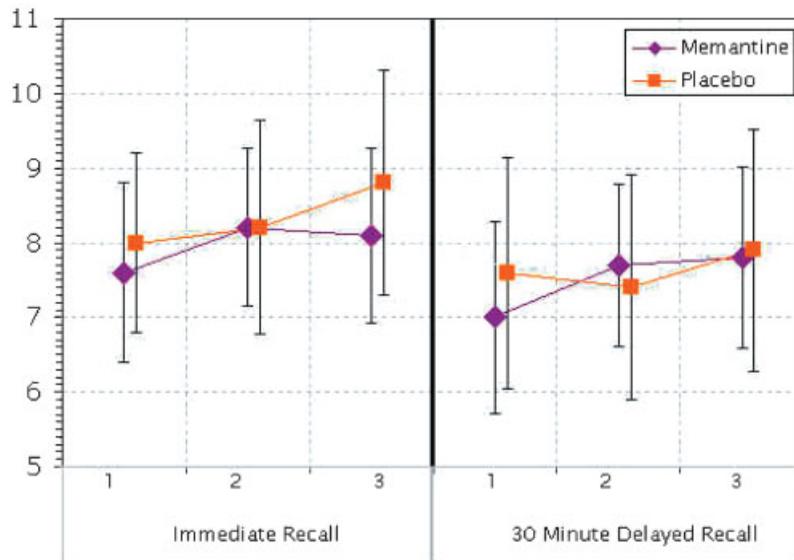


Figure 1. Comparison of treatment groups on Rey Auditory-Verbal Learning Test (immediate and delayed recall) after 1, 2, and 3 months of treatment

Psychologic Results at One, Two, and Three Months  
Mean response and 95% confidence intervals for Memantine and Placebo

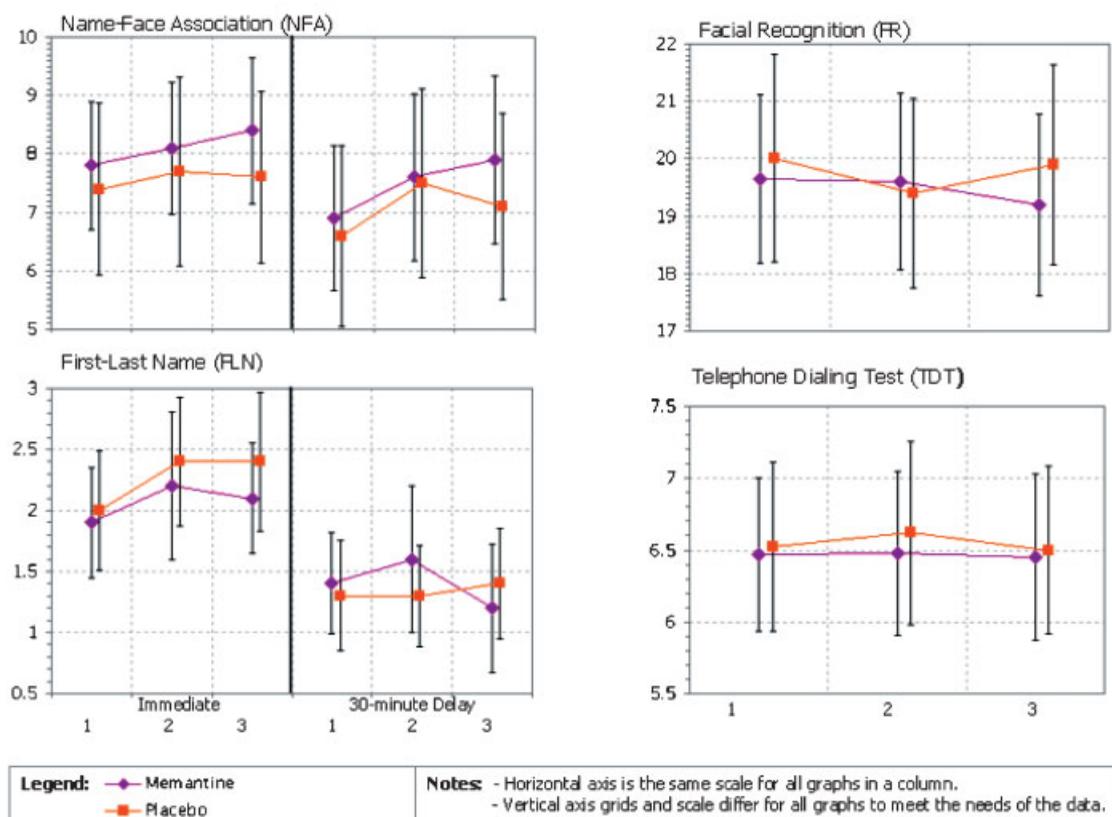


Figure 2. Comparison of treatment groups on memory tests from Psychologic Battery after 1, 2, and 3 months of treatment

no significant difference or trend on self-report of memory improvement.

#### CogScreen computerized test battery

A comparison of the treatment groups at each assessment period on the CogScreen Test battery is presented in Figure 3. The six CogScreen variables shown in Figure 3 have differences between treatment groups of  $p < 0.10$  at one or more visits. Table 3 provides statistical details.

For all scores shown in Table 3, memantine patients improved relative to those treated with placebo. For Matching-to-Sample accuracy and throughput (MTSACC and MTSPUT), Figure 3 shows the average Memantine scores are improved at all three visits. Table 3 shows the  $p$ -values are less than 0.10 for all three visits. For Matching-to-Sample speed

(MTSRTC), the memantine averages are lower (faster) for all three visits. Table 3 shows the  $p$ -value after three months of treatment is 0.095. For Symbol Digit Coding throughput (SDCPUT), average memantine scores are higher at all visits, and have a  $p$ -value of 0.092 at two months. For Symbol Digit Coding accuracy (SDCACC), average memantine scores are higher at all visits, and have a  $p$ -value of 0.049 at 3 months. For the visual monitoring task (DATRTC), mean reaction time for memantine is lower (i.e. faster) at all visits, and the  $p$ -value at 3 months is 0.056.

#### Adverse events safety analyses

A comparison of the two treatment groups on adverse event frequency is provided in Table 4 and the groups are compared on most frequently reported adverse events in Table 5.

### Selected Cogscreen Results at Baseline, One, Two, and Three Months

Adjusted Mean response and 95% confidence intervals for Memantine and Placebo.

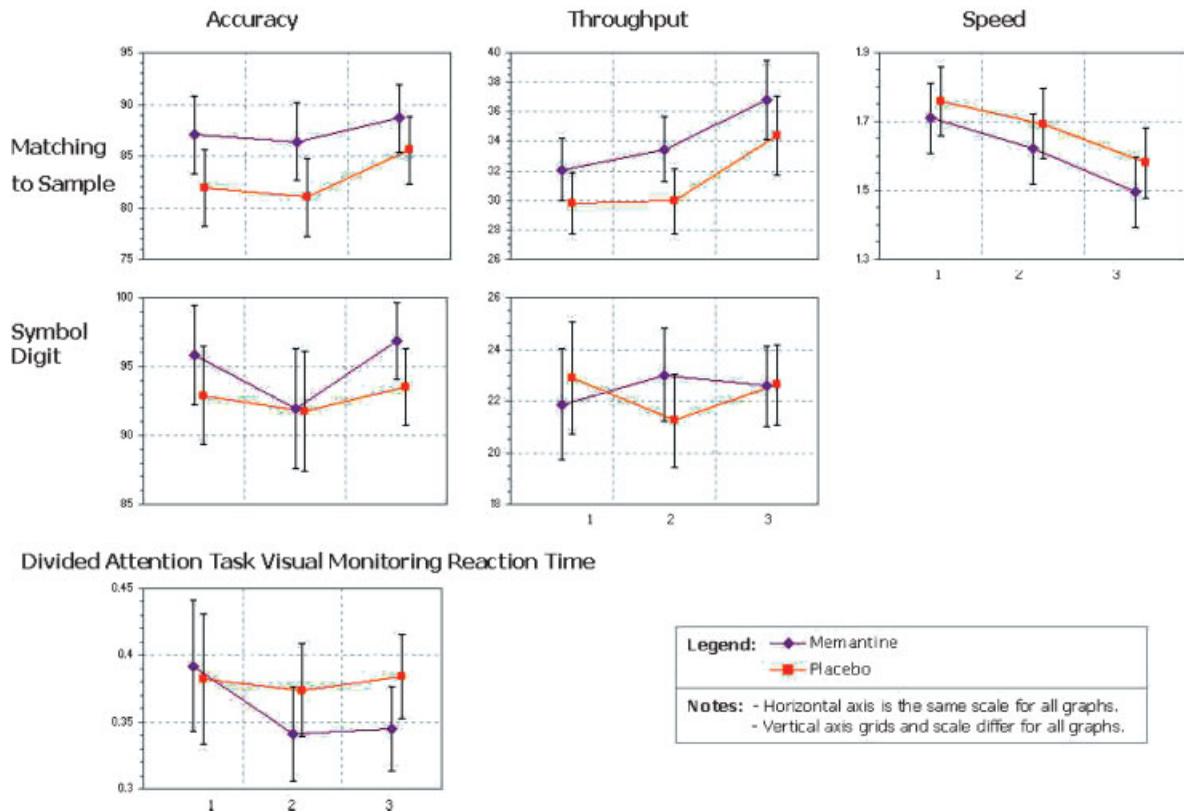


Figure 3. Comparison of Treatment Groups on Tests from the CogScreen Test Battery after One, Two, and Three Months of Treatment

## DISCUSSION

Results suggest that the memantine may improve attentional processes and information processing speed in subjects over age 50 with Age-Associated

Memory Impairment (AAMI). Trends and significant differences were seen on two measures of processing speed after one month of treatment, on three measures after 2 months, and on five measures after 3 months (Table 3). The total number of attentional variables assessed was ten. With a larger sample, significant results might be expected on all of these tests and possibly on others where differences were at or near the  $p = 0.10$  level. The trend toward greater improvement with time was apparent over 3 months

Table 3. ANCOVA comparisons of Memantine and Placebo on which a trend ( $p < 0.10$ ) was seen on a CogScreen score

Treatment duration	CogScreen Score	F	P
1 month	MTSACC	3.66	0.031
	MTSPUT	2.20	0.073
2 months	MTSACC	4.03	0.025
	MTSPUT	4.74	0.017
	SDCPUT	1.83	0.092
3 months	MTSACC	2.11	0.077
	MTSPUT	2.44	0.063
	MTSRTC	1.77	0.095
	SDCACC	2.86	0.049
	DATIRTC	2.64	0.056

Table 4. Overall comparison of memantine and placebo groups on frequency and severity of adverse experiences

Severity	Memantine (n = 30)	Placebo (n = 30)
None	11 (36.7%)	10 (33.3%)
Mild	11 (36.7%)	14 (46.7%)
Moderate	8 (26.7%)	6 (20%)
Severe	0	0

Table 5. Overall comparison of memantine and placebo and placebo groups on most frequently reported adverse experiences

Adverse experience	Memantine ( <i>n</i> = 30)	Placebo ( <i>n</i> = 30)
Infections	6 (20%)	8 (26.6%)
Gastrointestinal disorders	4 (13.3%)	6 (20%)
Nasopharyngitis	4 (13.3%)	4 (13.3%)
Nervous system disorder	1 (3.3%)	4 (13.3%)

and it is possible that treatment beyond 3 months would have led to even greater improvement.

These attentional and processing speed effects might be expected to improve performance on many cognitive tasks of daily life. For example, the battery on which effects were seen is used by the Federal Aviation Administration and by US and international airlines to determine the ability of pilots to perform the cognitive tasks involved in safe aircraft operation. It is also widely used by the military to assess abilities of individuals to perform various tasks that involve high-speed, high-reliability cognitive and psychomotor tasks. The tests are sensitive both to adverse cognitive drug effects (e.g. anticholinergic and sedative) and to the effects of compounds such as amphetamine that can improve performance under some circumstances (Kay *et al.*, 2005).

Complaints of memory loss and objective evidence of 'normal' memory loss were required for admission to this study but, contrary to expectations, the primary cognitive effects seen with memantine treatment were not on tests of memory. Indeed, we saw no significant effects or trends on either immediate or delayed recall on a standard memory test, the Rey Auditory Verbal Learning Test, on any of the four memory tests in the Psycholix computerized battery, or on the memory subtests in the Cogscreen battery. In all, eight memory test scores were evaluated as outcome measures at each assessment period. In subjects with AAMI, it does not appear that memory is the cognitive domain through which memantine produces behavioral effects.

The observation that the primary cognitive effects of memantine were on attention rather than memory is

#### KEY POINT

- Memantine does not appear to improve memory in Age-Associated Memory Impairment, but may improve attentional processes.

consistent with the expected effects of an NMDA receptor antagonist and consistent with findings in AD (Rogawski and Wenk, 2003).

Memantine was well tolerated in these non-demented subjects and adverse effects were equally common in the memantine and placebo groups.

#### ACKNOWLEDGEMENTS

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