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Using Biomarkers to Predict Memantine Effects in Alzheimer's Disease: A Proposal and Proof-Of-Concept Demonstration

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Abstract

Memantine's benefits in Alzheimer's disease (AD) are modest and heterogeneous. We tested the feasibility of using sensitivity to acute memantine challenge to predict an individual's clinical response. Eight participants completed a double-blind challenge study of memantine (placebo versus 20 mg) effects on autonomic, subjective, cognitive, and neurophysiological measures, followed by a 24-week unblinded active-dose therapeutic trial (10 mg bid). Study participation was well tolerated. Subgroups based on memantine sensitivity on specific laboratory measures differed in their clinical response to memantine, some by large effect sizes. It appears feasible to use biomarkers to predict clinical sensitivity to memantine.

Keywords

Alzheimer's disease; event-related potentials; memantine; neurocognition; prepulse inhibition

INTRODUCTION

The need for effective treatments for Alzheimer's disease (AD) is paramount [1]. The noncompetitive N-methyl-D-aspartate antagonist, memantine (MEM) is approved to treat moderate-to-severe AD and is often prescribed in earlier stages [2–5]. Though only used in a minority of AD patients, MEM adherence rates at 1 -year and beyond are highest among all

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SUPPLEMENTARY MATERIAL

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AD treatments [6]. MEM slows cognitive impairment in AD [3, 4, 7–10], but these benefits are modest and heterogeneous: many patients show little or no gains even after extended MEM trials. One way to enhance MEM efficacy might be to narrow the target population to more selective “sensitive” clinical subgroups identified via laboratory-based biomarkers [11].

MEM acutely enhances measures of early auditory information processing (EAIP) in healthy subjects (HS) and schizophrenia patients, with effects ranging from small to large [12–14, 16]. EAIP measures assess neurophysiological responses to highly structured auditory stimuli and are known to mediate neurocognition in schizophrenia patients [15]. Others have reported that MEM enhances similar neurophysiological measures in both HS [17] and laboratory animals [18–20].

Measures of acute “MEM sensitivity” might reflect many physiological variables—from drug absorption and CNS penetrance to receptor occupancy and beyond—that could make individuals more likely to benefit clinically from MEM. Neurophysiological and related changes in response to acute MEM challenge also suggest that MEM is bioactive and may access neural mechanisms relevant to neurocognition, and that such circuitry remains a viable drug target. Conceivably, an acute MEM challenge can be used to stratify AD patients as “MEM-sensitive” versus “MEM-insensitive”; this “personalized medicine” approach has been applied to other treatments [21–23] including psychotherapeutics [24, 25].

Here, we describe our study design and initial “proof-of-concept” and feasibility results from eight AD patients who completed measures of acute “MEM sensitivity”, followed by an open-label therapeutic trial with MEM. This report highlights results from four categories of measures: autonomic, subjective, cognitive, and neurophysiological.

METHODS

This study was approved by the UCSD Human Subjects IRB (protocol #172053). Eight participants with diagnoses of AD met inclusion criteria (Table 1). Screening included a medical history, physical examination, and electrocardiogram. Neurocognitive tests included the Mini-Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA), the Alzheimer’s Disease Assessment ScaleCognitive Subscale (ADAS-cog; primary outcome measure), the Neuropsychiatric Inventory Questionnaire and the Geriatric Depression Scale (NPI-Q and GDS; secondary outcome measures); for ADAS-cog, GDS and NPI-Q, higher scores reflect greater deficits. Blood was obtained for future analyses including genes associated with MEM sensitivity [25–27].

Tests of acute MEM sensitivity followed 7 and 14 days later (Fig. 1). At 0900, subjects ingested either placebo or MEM (20 mg) in a double-blind, pseudorandomized balanced order. Vital signs and subjective ratings were collected at regular intervals. The dose and time course were based on past studies [12, 13, 16].

Methods for neurophysiological measures are found in the Supplementary Methods. At 210 min post-pill, prepulse inhibition (PPI, a metric of sensorimotor gating) was measured [12]; 275 min post-pill, subjects completed the Repeatable Battery for the Assessment of

Neuropsychological Status (RBANS) [29]; 345 min post-pill, EEG was acquired: specific measures included mismatch negativity (MMN), P3a amplitude, ASSR (auditory steady state power and coherence), and excitatory/inhibitory index (E/I, reflecting the balance of cortical excitation and inhibition) based on fronto-central (FC) recordings. Previous studies reported significant gains in PPI, MMN, ASSR, and E/I index after one pill of MEM (20 mg) in HS and schizophrenia patients [12–14]. After each test day, subjects "guessed" whether they received placebo or MEM but were not given feedback.

Starting 7 d after testing, subjects titrated to 10 mg bid of MEM (unblinded) over 3 weeks. Eight, 16, and 24 weeks after reaching target dose, subjects were evaluated via primary and secondary outcome measures and a physical examination. One subject reduced her dose to 15 mg/d due to mild gait instability. Two subjects discontinued MEM: one after week 8 due to tinnitus (a pre-existing condition) and another at week 16 due to caregiver illness; for these subjects, last outcome values were "carried forward".

Outcome and laboratory measures were treated as continuous variables. We assessed MEM-induced changes in outcome measures (8-, 16-, and 24-week scores minus baseline for total ADAS-cog, GDS, and NPI-Q scores; positive numbers represent clinical deterioration) and used a median split to categorize subjects with the greatest versus least MEM-induced changes in laboratory measures. For this "proof of concept" demonstration, Cohen's "d" sizes are reported $(mean_1\text{-}mean_2)/SD_{pooled}$); where informative, repeated measure analysis of variance (ANOVA) was used to generate F and p values for group differences, and parametric and non-parametric analyses were used to assess correlations.

RESULTS

All subjects were impaired by AD symptoms (MoCA mean 16.6; range: 6–23). Mean ADAS-cog scores increased modestly over time (baseline versus week 24, $d = 0.21$). Neither GDS nor NPI-Q exhibited consistent change-from-baseline over the 24-week trial.

Acute effects of MEM on laboratory measures ranged from large (subjective and autonomic measures) to small (neurophysiological measures) (Supplementary Table 1A, B). Analyses assessed the relationship between acute MEM-induced changes in autonomic, subjective, cognitive, and neurophysiological measures versus outcome measures at weeks 8–24:

1. Mean autonomic changes after placebo versus 20 mg MEM were small. Despite this, individual differences in sensitivity to these MEM effects appeared informative. For example, subjects who averaged acute MEM-induced reductions in heart rate (HR) experienced a 16-week delay in cognitive deterioration, compared to subjects who averaged acute MEM-induced increases in HR (Fig. 2A). Salutary effects of MEM on GDS scores were also noted among subjects experiencing acute MEM-induced reductions in HR ($d = 0.65$ by week 24).
2. Subjective measures identified acute MEM effects on aversive and positive hedonic ratings; MEM ratings exceeded placebo by more than 20% only on "happy" ratings. Subjects reporting less MEM-associated drowsiness experienced a more favorable ADAS-cog response; subjects reporting greater

"happy" levels and lower "anxiety" levels after acute MEM were most likely to experience reductions (improvements) in NPI-Q and GDS scores, respectively, during treatment (NPI-Q: Fig. 2B). Among subjects who correctly guessed that they had received the active pill, gains in all outcome measures arithmetically exceeded those of subjects who failed to correctly identify their active pill, with medium-to-large effect sizes (NPI-Q: Fig. 2C).

3. Cognition: As a group, subjects showed no effect of acute MEM on RBANS total scale index score (means: placebo = 70.13, MEM = 69.75). Compared to subjects whose RBANS scores declined after acute MEM challenge, those with more positive changes in RBANS tended to exhibit a more positive clinical (ADAS-cog, GDS) response to MEM treatment (ADAS-cog: Fig. 2D).

4. Neurophysiological measures: With this small sample, two neurophysiological measures modestly distinguished MEM "responders" versus "non-responders": PPI and FC E/I. Subjects exhibiting greatest MEM-induced gains in PPI experienced a 16-week delay in cognitive deterioration, compared to subjects least sensitive to MEM-induced PPI gains. Group differences were medium-to-large at weeks 8 ($d = 0.60$) and 16 ($d = 0.74$). However, by week 24, any "delay" in cognitive deterioration among subjects with MEM-enhanced PPI had waned. Subjects with the least PPI MEM sensitivity showed stable, modest GDS scores across the 24-week trial, while subjects with the greatest PPI sensitivity exhibited steady reductions in GDS scores; by week 24, this difference reached a large effect size ($d = 1.20$) (Fig. 2E).

Analysis of ADAS-cog changes versus median split of acute changes in FC E/I index revealed results identical to those detected with changes in both HR and "drowsy" ratings (above): an overall rise in ADAS-cog scores that was delayed in "high" versus "low" FC E/I responders (E/I sensitivity x week: $p < 0.02$) and large effect size differences at weeks 8 ($d = 1.38$) and 16 ($d = 0.91$) but not 24. These convergent patterns among sensitivity measures reflected a correlation between acute MEM-induced changes in FC E/I and those in both HR ($r = -0.92$) and "drowsy" ratings ($r = -0.61$).

DISCUSSION

We describe a novel strategy for identifying AD patients who are more versus less likely to benefit clinically from MEM, using a challenge dose in a laboratory setting to assess MEM effects on specific potential biomarkers. The reasoning behind this strategy is straightforward: the clinical response to MEM is heterogeneous and some of the variance associated with this response should reflect characteristics of an individual's physiology that may be detectable based on their sensitivity to a challenge dose of MEM.

One important concept to emerge from this demonstration is that biomarkers might predict an individual's MEM sensitivity even if these variables do not detect group differences in response to MEM challenge. For example, changes in autonomic and subjective responses after acute MEM challenge were predictably small, but MEM sensitivity in these responses exhibited variability across the 8 subjects that appeared to be related to clinical sensitivity.

Acute MEM-induced changes in several measures—HR, drowsiness, RBANS performance, PPI, and FC E/I—were associated with a 16-week delay in ADAS-cog progression, but for most of these measures, this delay was completely reversed by week 24. This was not the pattern with changes in GDS or NPI-Q scores, for which early benefits often persisted or increased over the duration of the study.

We selected several experimental parameters based on known acute MEM effects in HS and schizophrenia patients [13, 14, 16, 17], using measures that are feasible to assess in AD patients [30–39]. Conceivably, other neurophysiological measures, or dose-response and time course studies in AD patients, might produce a more informative battery for predicting clinical sensitivity. Versions of the selected EMG- and EEG-based measures have been studied previously in AD cohorts, and (in contrast to schizophrenia) levels in AD patients generally equaled, or in the case of ASSR exceeded, levels in HS [33].

A pragmatic predictive model for clinical practice might differ from the present design in several ways. First, rather than using a median split to define MEM sensitivity, a pragmatic design might identify a threshold for MEM sensitivity, based, for example, on a percent gain from baseline levels, or on population-based normal ranges of MEM effects. Alternatively, the model might utilize predictive algorithms with multiple measures, clinical variables, blood levels, and genetic markers that are increasingly available in clinical practice. Second, the two laboratory test days (placebo versus MEM) might be collapsed to a single-day pre- versus post-MEM design, in which baseline measures are acquired before MEM administration, followed by post-MEM measures. This design would abandon both blinding and order randomization—suboptimal because it might confound subjective measures. Third, the laboratory measures would be pared for maximal efficiency and reliability. For example, while PPI is sensitive to MEM [12, 16], and in this small sample PPI sensitivity predicts clinical benefits, the utility of PPI for personalized medicine in AD may be limited by the high proportion of startle non-responders among older adults [40]; by contrast, attrition in EEG measures is near-zero. Furthermore, while multiple EAIP measures can be acquired with the same EEG configuration, PPI requires EMG electrodes and thus added preparation time and equipment. Finally, it is unclear whether the present outcome measures are most sensitive to the clinical benefits of MEM, or whether ADAS-cog subtests, or different measures of pro-cognitive changes, might be preferred for this predictive model.

Acute MEM did not impact cognitive performance in AD patients; we encountered this in schizophrenia patients [41], despite the fact that sustained MEM treatment in schizophrenia is associated with neurocognitive gains [42]. Conceivably, in both disorders, MEM-induced cognitive gains reflect an indirect process, requiring sustained direct effects on a basic brain mechanism (e.g., neural synchronization [13], sensorimotor gating [12], or auditory fidelity [43]) to produce gains in neurocognition, or in processes such as verbal communication [44–48].

This search for predictive biomarkers is largely agnostic to mechanism. Our preliminary results suggest that even low-tech subjective ratings after a MEM challenge might identify individuals most likely to benefit clinically from this medication. For example, subjects who correctly identified their active pill day (presumably reflecting subjective awareness of active

drug) benefitted most from MEM over the 24-week trial, with medium-to-large effect size advantages in all outcome measures. However, we have no expectation that the findings in these 8 AD subjects are definitive; rather, we expect that a fully-powered study will produce different results, both in terms of the measure (or groups of measures [49]) that optimally predicts MEM clinical sensitivity and in terms of issues that make us rethink aspects of model feasibility. Nevertheless, this proof-of-concept study provides a framework for the development of biologically-informed, personalized therapeutics for AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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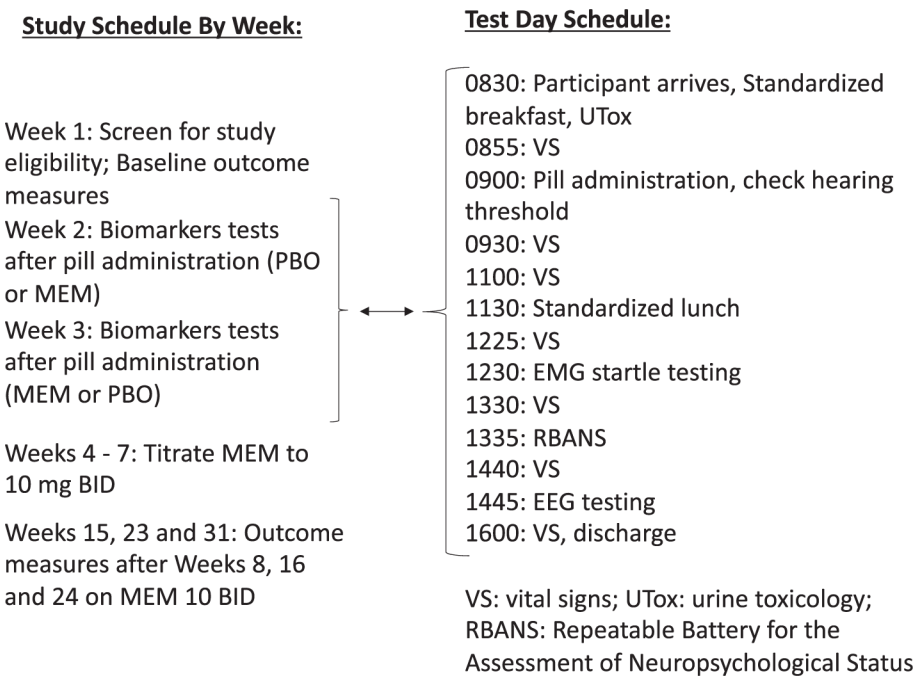

Fig. 1.

Study design and test schedule, described in the Methods. The study involved a screen day, two test days, and titration to 10 mg MEM bid for 24 weeks, with outcome measures after 8, 16, and 24 weeks. The detailed schedule of the two test days is shown at right: autonomic, subjective, neurocognitive, and neurophysiological measures were obtained on each test day after administration of either placebo or 20 mg MEM, in a double-blind, order-balanced design.

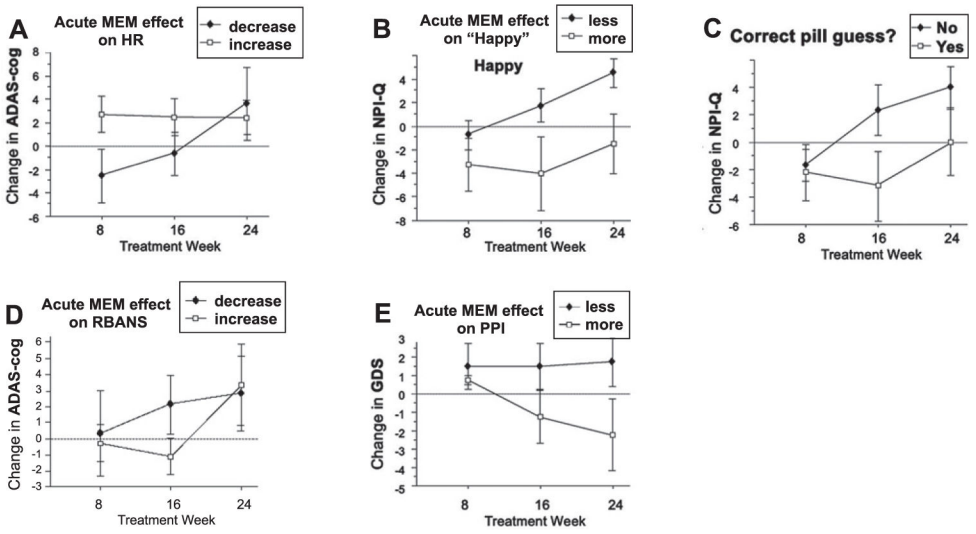

Fig. 2.

Five examples of changes from baseline clinical outcome measures (Y-Axis) after 8–24 weeks of MEM (10 mg bid), among subgroups defined by a low versus high (median split) response to acute MEM challenge (placebo versus 20 mg po). Larger Y-axis values reflect worsening of AD symptoms. A) Example of autonomic response to acute MEM challenge: Subjects with a mild bradycardic response to acute MEM challenge exhibited a 16-week delay in the progression of cognitive symptoms during MEM treatment (d = 1.38 and 0.91 at weeks 8 and 16, respectively). B) Example of subjective ratings after acute MEM challenge: Subjects who experienced the greatest "Happy" increase (shown here) and least "Anxiety" increase after acute MEM challenge were most likely to experience reductions in NPI-Q (shown here) and GDS scores, respectively. Less acute MEM-associated drowsiness predicted a positive cognitive (ADAS-cog) response to MEM. C) Example of pill "guess": More favorable responses to MEM were detected in measures of ADAS-cog, GDS, and NPI-Q (shown here) among subjects who did (n = 5) versus did not (n = 3) correctly guess pill identity on the day that they received active MEM dose (d = 0.41, 1.13, and 0.88 for ADAS-cog, GDS, and NPI-Q, respectively, averaged across weeks). "Correct guess" versus "incorrect guess" groups did not differ in baseline ADAS-cog or MoCA scores (both Fs < 1). D) Example of cognitive response to acute MEM challenge: Progression of ADAS-cog scores for weeks 8–24 among subjects whose RBANS index score declined after acute MEM (mean decline = 3.8) versus those that didn't decline (mean gain = 5.3) (d = 1.07 at week 16). This pattern was also seen for the GDS response to sustained MEM treatment (d = 1.17 at week 16). E) Example of neurophysiological response to acute MEM challenge: Subjects showing the greatest acute MEM-enhanced PPI exhibited greater gains in GDS scores (shown here; d = 1.20 by week 24) and a modestly delayed progression of cognitive deficits (d = 0.74 by week 16) and during MEM treatment. Two subjects had very low startle magnitude that would qualify them as "non-responders" in many studies of PPI (e.g., [12, 16]), but exclusion of these subjects did not impact the overall patterns of results. Subjects showing an acute MEM-induced increase in FC E/I also exhibited a 16-week delay

in deterioration of ADAS-cog performance (not shown: $d = 1.38$ and 0.91 for weeks 8 and 16, respectively).

Table 1

Participants

A. Participant Inclusion / Exclusion Criteria	
Inclusion	**Exclusion**
Established diagnosis of AD	Active systemic illness (e.g., heart disease, liver failure, renal insufficiency, cancer, HIV, tuberculosis, Hepatitis C)
MMSE score between 10–22 or MoCA score between 15–24	Current psychiatric or neurologic illness other than AD
Age 50–83	History of vascular disease, MI, CVA, TIA, seizure, head injury with sustained (>15 minutes) loss of consciousness
Has a knowledgeable caregiver available to accompany on laboratory visits	Substance dependence
Ambulatory	Past treatment with MEM; unable to tolerate donepezil
Medically stable	Investigational drug treatment ≤ 30 days before screening
Hearing threshold ≤ 45 db(A) at 1000 HZ average across right and left ear	Current medications include: amantadine, riluzole, other pro-cognitive medication (not including donepezil), or opiates
EKG reviewed by cardiologist and approved by PI as study appropriate	Positive UTox for non-prescribed psychoactive substance
Informed consent	Enrolled in cognitive remediation therapy
B. Participant characteristics (Mean (SEM))	
Age (y)	73; range = 68–80
Sex (M:F)	4:4
Education (y)	16.75 (0.53)
Ethnicity - Asian: American/Alaskan native: Caucasian: multiple	1:1:5:1
Marital status - married: divorced: widowed	6:1:1
Weight (lbs)	157.13 (8.61)
Smoking (Y:N)	0:8
Caffeine use (mg/day)	88.50 (36.55)
MoCA score	16.63; range = 6–23
Age first symptoms (y)	71.75 (1.79)
Time since first symptoms (y)	2.50 (0.50)
Taking prescription medications	7 (1 taking donepezil)