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Maintenance Treatment of Depression in Old Age: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined with Antidepressant Pharmacotherapy

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Abstract

Context—Cognitive impairment in late-life depression is a core feature of the illness.

Objective—to test whether donepezil + antidepressant is superior to placebo + antidepressant in (1) improving cognitive performance and instrumental activities of daily living and (2) reducing recurrences of depression over two years of maintenance treatment.

Design—Randomized, double-blind, placebo controlled maintenance trial.

Setting—university clinic

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Main Outcome Measures—global neuropsychological performance, cognitive instrumental ADL, and recurrent depression.

Results—Donepezil + antidepressant temporarily improved global cognition (treatment by time interaction $F = 3.78$, $df = 2$, 126 , $p = .03$), but effect sizes were small (Cohen's $d = 0.27$: group difference at 1 year). A marginal benefit to cognitive instrumental ADL was also observed (treatment by time interaction; $F = 2.94$; $df = 2$, 137 , $p = 0.06$). The donepezil group was more likely to experience recurrent major depression: 35% [95% CI: 24%, 46%] versus 19% [95% CI: 9%, 29%] (log rank chi squared = 3.97, $p = .05$); hazard ratio = 2.09 [95% CI: 1.00, 4.41]. Post-hoc subgroup analyses showed that, of 57 participants with mild cognitive impairment, 3/30 on donepezil (10%; 95% CI: 0, 21%) and 9/27 on placebo (33%; 95% CI: 16%, 51%) converted to dementia over two years (Fisher exact $p = 0.05$). The MCI subgroup had a 44 percent recurrence rate of major depression on donepezil versus 12% on placebo (LR=4.91, $p=.03$). The subgroup with normal cognition ($n = 73$) showed no benefit on donepezil or increase in recurrence of major depression.

Conclusion—Whether ChEI should be used as augmentation in the maintenance treatment of late-life depression depends upon a careful weighing of risks and benefits in those with MCI. In cognitively intact patients, donepezil appears to have no clear benefit for preventing progression to MCI/dementia or recurrence of depression.

BACKGROUND

Cognitive impairment in late-life depression is a core feature of the illness, contributing to disability and impaired quality of life. Even after remission, cognitive functions do not improve to levels seen in non-depressed subjects¹⁻³. Moreover, cognitive and functional impairment may progress. Depression is increasingly thought to be a possible risk factor for, or a prodrome to, dementing illnesses^{4, 5}.

We report here the efficacy and safety of combining a cholinesterase inhibitor (ChEI) with maintenance antidepressant pharmacotherapy over two years to improve global cognitive performance and cognitive instrumental activities of daily living (C-IADL) in older, non-demented adults with a recent major depressive episode. We chose ChEI therapy because of evidence that it may: (a) prevent symptomatic progression of mild cognitive impairment (MCI)⁶, especially in subjects with depressive symptoms⁷, (b) remediate cholinergic deficits and enhance cerebral blood flow — potentially an effect relevant to the pathogenesis of vascular dementia⁸ and, perhaps, depression⁹, and (c) modify amyloid precursor protein metabolism and have neuroprotective effects¹⁰. In addition, we chose donepezil because of its potential efficacy in MCI^{6, 7}, pharmacokinetic properties allowing once daily dosing, and generally good tolerability and safety data¹¹. RCTs comparing the FDA-approved ChEIs in Alzheimer's Disease suggest no major difference in therapeutic efficacy^{12, 13}.

One of the most consistent effects of ChEIs in Alzheimer's Disease is the improvement of neuropsychiatric symptoms such as apathy¹⁴⁻¹⁶ (although not agitation)¹⁷. Since executive dysfunction may increase the risk of depression recurrence¹⁸, it is possible that enhancement of executive functioning by donepezil could also protect patients from depression recurrence. At the same time, however, ChEIs may induce symptoms of depression because of cholinergic hypersensitivity conferred by depression^{19, 20}. Consistent with the proposed cholinergic role in the regulation of mood and affect is the recent finding that scopolamine produces a rapid and robust antidepressant response, possibly via modulation of N-methyl-D-aspartate receptor function²¹. We expected that a depressogenic effect of donepezil would be less likely than positive behavioral effects in participants already in remission from their depressive episodes and on maintenance antidepressant pharmacotherapy.

Our primary hypotheses were that donepezil + antidepressant in older non-demented adults with a recent major depressive episode would be superior to placebo + antidepressant in (1) improving global cognitive performance and cognitive IADLs over a two-year period; and (2) reducing recurrences of major depression. We did not have an *a priori* hypothesis that donepezil would reduce rates of conversion to dementia in depressed subjects with MCI, in light of the Cochran review conclusions of donepezil's modest effects and side effect burden in MCI.¹³

METHODS

Overview

Participants received two phases of treatment: (a) 12-16 weeks of open antidepressant pharmacotherapy with supportive depression care management to bring about response and thereby to establish eligibility for (b) the randomized, placebo-controlled maintenance phase of treatment (2 years). Following antidepressant response during the first phase, participants had baseline neuropsychological, cognitive IADL assessment, and adjudication of cognitive status (normal, MCI, dementia) by the University of Pittsburgh Alzheimer's Disease Research Center (ADRC). Subjects were then randomized and had repeated neuropsychological and IADL assessment 12 and 24 months later. The protocol was approved by the Institutional Review Board of the University of Pittsburgh, and all subjects provided written informed consent.

Depressed Participants

We screened and recruited 299 adults aged 65 and older from primary care practices, mental health clinics, other federally sponsored clinical research projects, and advertisements (Figure 1). 220 qualified for participation and signed consent. 158 responded to open antidepressant treatment and completed assessment for the randomized controlled trial. 130 eligible subjects agreed to randomization. The first depressed subject entered in 4/04, and the last exited in 9/09.

To qualify, subjects needed to be: (a) 65 or older, (b) in a non-bipolar, non-psychotic major depressive episode 22, (c) with a score of ≥ 15 on the 17-item Hamilton Rating Scale for Depression (HAM-D) 23, and (d) either cognitively normal or with MCI. We included cognitively normal subjects because major depressive disorder in later life frequently heralds the onset of MCI (25%-30% within 12 months) and subsequent dementia.^{3, 24, 25} The question addressed is whether donepezil protects cognitively normal patients from developing MCI. We included subjects with MCI to test for cognitive improvement on donepezil. We report both primary analyses of the aggregate group of all participants ($n = 130$), as well as post-hoc analyses of the two subgroups who were either cognitively normal ($n = 73$) or who were adjudicated to have Mild Cognitive Impairment ($n = 57$) at the start of maintenance treatment. Participants with dementia were excluded, as were those with substance use disorders. Informant information was used in assessing subjects' behavior and cognitive functioning. In general, subjects had mildly to moderately severe major depression and could be safely treated as outpatients.

The ADRC Consensus Conference (co-investigators OL and STD) utilized post-depression remission neuropsychological data, clinical history, MRI data, and PASS data²⁶ (Performance Assessment of Self-Care Skills). The following diagnoses were made according to National Alzheimer Coordinating Center criteria²⁷: no cognitive disorder, MCI amnesic-single domain, MCI amnesic-multiple domain, MCI nonamnesic-single domain, MCI nonamnesic-multiple domain, and dementia. Any participant found to be

demented at baseline or to have become demented at 12 or 24 months follow-up was removed from the study and offered open treatment with donepezil.

We tested for APOE alleles (co-investigator MIK) using a previously published method.²⁸ These data were available in 102 of 130 randomized subjects. We examined the association between APOE*4 carrier status and MCI and with donepezil effects on cognition and mood.

Assessment and Primary Outcome Measures

Primary outcome measures were (a) a global measure of neuropsychological functioning, (b) a composite measure of cognitive instrumental activities of daily living, and (c) recurrence of major depression.

Neuropsychological functioning was assessed with 17 well established and validated individual tests measuring multiple domains (Table 1). We transformed raw scores for individual tests into Z-scores using the baseline distribution of a non-depressed, cognitively normal, older-adult comparison group (n = 36) of similar age, education and medical health recruited concurrently with the depressed participants. These Z-scores were averaged within each neuropsychological area to produce domain scores and then averaged over all 17 tests to calculate a global performance score. .

We explored the effect of donepezil and placebo on five domains of neuropsychological functioning; speed of information processing, executive functioning, delayed memory, language, and visuo-spatial function. The component tests of each domain are presented in Table 1 and are the same as those previously reported by Butters et al.,²⁹ with the exception that the modified Rey-Osterreith Figure Copy replaced Clock Drawing. We computed the following Cronbach's alpha coefficients for each domain: language (0.73), visuospatial (0.67), memory (0.66), executive (0.73), and speed of information processing (0.79).

Instrumental Activities of Daily Living (IADL)—We administered the PASS self-report measures of habit (“does do”) and the PASS criterion-referenced observational measurement performed in subjects’ homes (“can do”).^{7, 26, 30} The PASS is a performance-based assessment of 26 daily living activities involving functional mobility, personal care, and instrumental activities having a cognitive (e.g., medication management) or physical (e.g., changing bed linens) emphasis. A clinician rater observes patients perform each task and rates them according to pre-determined criteria on a 4-point ordinal scale, ranging from 0 (unable) to 3 (independent). Levels of assistance are rated on a 9-point hierarchy consisting of three levels each of verbal, gestural, and physical assists. A composite measure of thirteen cognitive IADL items included performance on activities such as shopping (cash exchange), bill paying, medication management, and home safety. Distribution of the cognitive IADL composite measures was dichotomous: participants either had independent performance or they did not. We report the percentage of subjects at each assessment point with independent functioning.

Recurrent Episodes of Major Depression—As in our previous maintenance therapy trials^{31, 32}, recurrence of major depression was defined using SCID/DSM-IV criteria²², a Hamilton depression score (17-item)²³ of 15 or higher over two consecutive weeks, and confirmation by a geriatric psychiatrist not involved in the participant’s treatment.

Randomization and Masking

A computer-generated random assignment sequence using permuted blocks of 4 or 2 (depending on site) was stratified by site of recruitment (mental health specialty clinic versus primary care), cognitive status (MCI present/absent), and use of rescue medication

(SNRI, aripiprazole) during initial open treatment. The randomization list was prepared in advance by our statistician (SM). Only the research pharmacist had access to the randomization list. The blind was not broken until outcome analyses had been completed. Neuropsychological function, cognitive IADL, and clinical status were evaluated by independent assessors who were blind to participants' randomized treatment assignment and baseline cognitive status (MCI present/absent). Identical capsules of donepezil (5 mg, 10 mg) and placebo were provided gratis by Pfizer/Eisai.

Intervention

To qualify for randomization to donepezil or placebo, full antidepressant response was required (defined as a Hamilton score of 10 or less for three consecutive weeks). Patients initially received open antidepressant pharmacotherapy with escitalopram (up to 20 mg/day). Those not responding fully were switched to a serotonin noradrenergic reuptake inhibitor (SNRI: duloxetine, up to 120 mg/day), followed as needed by aripiprazole augmentation (up to 15 mg/day) to achieve full response. The goal of using this algorithm was to increase the number of subjects available to participate in the maintenance phase of the trial, a precondition of which was full response to initial antidepressant pharmacotherapy. The distribution of antidepressant treatment regimens was similar in both maintenance conditions, with over 80% of subjects receiving either escitalopram or rescue, second-line pharmacotherapy using duloxetine. That is, the percentage of subjects receiving second-line ("rescue") pharmacotherapy did not differ between the two maintenance arms of the study. The antidepressant regimen associated with full response was continued during maintenance treatment, unless a subject experienced recurrence. To allow completion of the 2-year study, we treated recurrences using higher doses or switching from escitalopram to SNRI. Most of the recurrent episodes (24/28, 85.7%) were treated to response. We encouraged adherence to antidepressant pharmacotherapy at each clinic visit to assure maximal benefit. We tracked adherence by asking what percentage of their doses subjects had taken since the last clinic visit.

Sixty-seven subjects were randomized to donepezil and 63 to placebo. The mean (SD) dose of donepezil at study exit was 7.8 (2.5) mg/daily (mostly AM dosing), with 37/67 donepezil subjects on 10 mg daily and 30 on 5 mg daily (they were unable to tolerate a full dose due mainly to GI side effects and vivid dreams or other sleep disturbances).

Statistical Analyses

We followed the intention-to-treat principle: all randomized participants and all follow-up assessments were considered in the analyses. Analyses were performed by study statisticians in the Graduate School of Public Health (SJA, SM) and in the Department of Psychiatry (PRH, AEB). The study sponsors played no role in the outcomes analysis.

Primary Analysis: Donepezil Effects on Cognition and Depression Recurrence in the Combined Group of Cognitively Normal and Mildly Cognitively Impaired Participants

The primary analysis of changes in outcome measures over two years was a repeated-measures mixed effects model with both treatment and time as main fixed effects. To control for baseline cognitive classification, MCI classification was entered as a covariate along with all two-way interactions and the three-way interaction. In the analysis of the neuropsychological measures, we used the PROC Mixed procedure. In the analysis of the dichotomized PASS data (independent versus assisted performance), we used a logistic link function in the PROC GLIMMIX procedure. All statistical analyses were conducted using the SAS version 9.2.

We used Kaplan-Meier (KM) curves to quantify the percentage of participants who were free of depression recurrence over time³³. Cox proportional hazard (PH) models quantified hazard ratios (HR) comparing the two treatment groups. Tests of proportionality were conducted via the method proposed by Grambsch and Therneau³⁴ and, in all cases, indicated that proportionality assumptions were valid. Formal tests of treatment by MCI interaction and treatment effectiveness for MCI and cognitively normal participants were conducted using Cox PH models.

To adjust for participants who had permanently dropped out of the study, we classified terminations as being due either to study design (for example, adjudication of dementia) or to any other type of termination (for example, adverse events). We compared the temporal patterns of termination status by treatment arm for each type of termination, by examining cumulative incidence curves which adjusted for the competing causes of termination³⁵. All intermittent missing values were considered missing at random (MAR).

No significant treatment difference for terminations by study design was observed; however a significant treatment effect for all other terminations was noted ($p = .03$). Treatment difference in termination not by study design was found mostly in subjects with MCI. Consequently, we conditioned on MCI status in the mixed effect model to account for this covariate-dependent missingness mechanism for both neuropsychological functioning and cognitive instrumental activities of daily living.

Post-hoc Analysis: Donepezil Effects on Subgroups of Cognitively Normal and Mildly Cognitively Impaired Participants

We used the Fisher exact test to compare rates of dementia conversion and depression recurrence in subgroups of cognitively normal ($n = 73$) and mildly cognitively impaired ($n = 57$) subjects, while under randomized maintenance treatment with donepezil or placebo augmentation of maintenance antidepressant pharmacotherapy.

RESULTS

A. Primary Analyses

As shown in Table 1, donepezil subjects did not differ from those on placebo in age, gender, race, years of education, depression scores at baseline and randomization, medical burden (Cumulative Illness Rating Scale)³⁶, cognitive status (Mini-Mental Status Exam)³⁷, or baseline Z-scores for global cognition and each of the five domain scores. The distribution of ADRC diagnoses (normal cognition, subtypes of Mild Cognitive Impairment) also did not differ. The types of antidepressant pharmacotherapy were similar in the two treatment arms.

Neuropsychological performance (Table 2, Figure 2)—The groups changed at different rates over time, with the donepezil group showing a temporary advantage in global cognition at one year that was not sustained at two years (treatment x time interaction $F = 3.78$, $df = 2$, 126 $p = 0.03$). However, group difference effect sizes were small at one year (Cohen's $d = 0.27$) and at two years (Cohen's $d < 0.05$) and not statistically significant. As shown in Table 2 and Figure 2, two domains of cognitive functioning demonstrated treatment by time interaction: executive function ($F = 6.93$; $DF = 2,126$; $p = 0.001$) and memory ($F = 3.93$; $DF = 2,123$; $p = 0.02$). In addition, language demonstrated a higher-order interaction of treatment, time, and MCI status ($F = 3.14$; $DF = 2,126$, $p = 0.05$)

Instrumental activities of daily living with a cognitive emphasis (C-IADL)

Performance on cognitive IADL tasks showed a marginally different pattern of change over time in subjects receiving donepezil vs. placebo (treatment x time interaction $F = 2.94$, $df =$

2, 137, $p = 0.06$). The percentage of subjects on donepezil reporting independent task performance at 12 months (Cohen's $d = 0.20$, $p = 0.27$) and at 24 months ($d = 0.29$, $p = 0.11$) did not differ from placebo. We did not detect differential effects of donepezil over time on task performance observed in subjects' homes (treatment x time interaction $F = 0.93$, $df = 2$, 136, $p = .40$).

Recurrence of major depressive episodes (Figure 3)—The recurrence percentages by two years were 35% [95% CI: 24%, 46%] on donepezil and 19% [95% CI: 9%, 29%] on placebo (log rank chi squared = 3.97, $p = .05$; HR = 2.09 [95% CI: 1.00, 4.41]).

B. Post-Hoc Analyses of Dementia Conversion and Depression Recurrence in Cognitively Normal and Mildly Cognitively Impaired Subgroups

Thirteen of all 130 subjects (10%) converted to dementia over two years: 1 who had been cognitively normal at the start of maintenance treatment and the remaining 12 who had had Mild Cognitive Impairment. Thus, 12/57, or 21.1% of the subgroup with MCI, converted to dementia: 3/30 (10%; 95% CI: 0, 21) on donepezil and 9/27 (33%; 95% CI: 16%, 51%) on placebo; Fisher exact $p = .05$. There was a trend for APOE*4 carriers to be over-represented among those with MCI at baseline (12/43) versus those with normal cognition (8/59): Fisher exact $p = 0.08$. With respect to types of dementia adjudicated by the ADRC, 8/12 had AD probable, two had AD possible, one had fronto-temporal dementia, and one 'dementia/other.' Five of 11 MCI subjects with APOE data were APOE*4 carriers (one 2/4, four 3/4). In the subgroup with normal cognition at the start of maintenance treatment ($n = 73$), 6/37 (16.2%) on donepezil experienced cognitive decline (that is, five developed MCI and one, dementia), and 8/36 (22.2%) on placebo showed cognitive decline (all MCI) (Fisher exact $p = 0.56$). In contrast to those showing cognitive decline, 7 of the 57 with MCI at the start of maintenance treatment were adjudicated to have reverted to normal cognition on follow-up

In the MCI subgroup, 8/30 on donepezil had recurrence of major depression over two years versus 3/27 on placebo: 44% [95% CI: 28%, 60%] versus 12% [95% CI: 1%, 23%] (log rank chi squared = 4.91, $p = .03$). See figure 3. In the cognitively normal subgroup, 11/37 on donepezil had recurrence versus 8/36 on placebo: NS. Recurrence was not significantly affected by dose of donepezil (5 mg versus 10 mg) (LR = 0.43, $p = .51$). Two subjects on donepezil developed mania (in the absence of a history of bipolar spectrum disorders), and a third subject (with a history of suicidal ideation) attempted suicide by overdose. (See Figure 1 for summary of adverse events associated with donepezil and placebo.)

In further exploratory analyses, we observed a trend for a greater proportion of those who experienced recurrence to have received second-line or rescue antidepressant pharmacotherapy (with SNRI, aripiprazole) following only partial response to escitalopram during phase 1. Specifically, 17/30 who experienced recurrence (56.7%) versus 38/100 who did not experience recurrence (38%) received second-line pharmacotherapy (Fisher exact $p = 0.09$). However, the proportion receiving rescue pharmacotherapy did not differ between those randomized to donepezil (29/67) and placebo (26/63): Fisher exact $p = 0.86$ (thus suggesting that recurrence was related to the use of donepezil and not to depression treatment refractoriness). Sally, please highlight in yellow the information contained in parentheses in the preceding sentence The two groups (recurrence yes/no) did not differ in the distribution of APOE alleles (Fisher exact $p = 0.21$); 19% of both those with recurrence (5/26) and those without (15/76) were APOE*4 carriers. Amnestic and non-amnestic MCI subjects also did not differ in the proportion experiencing recurrence of major depression: 6/35 and 5/22, respectively (Fisher exact $p = .73$). Of the 30 participants who experienced recurrence, 24 of 28 (85.7%) were treated to response (Hamilton Depression Rating Scale score of 10 or less over three consecutive weeks).

CONCLUSIONS

This is the first confirmatory RCT of ChEI augmentation in older non-demented adults with a recent major depressive episode. Our primary analyses indicated a temporary positive effects of donepezil on global cognitive function (as well as on domain-specific measures of executive function and memory), marginal effects on a composite measure of cognitive instrumental activities of daily living, and, in a post-hoc subgroup analysis of those with MCI, a lower rate of conversion to dementia over two years (33% on placebo versus 10% on donepezil). However, co-administration of donepezil also led to higher rates of recurrent depressive episodes (35% versus 19% in the entire group of participants; and 45% versus 12% in the MCI subgroup), despite the use of maintenance antidepressant pharmacotherapy. The clinical significance of increased affective episodes is not only the suffering and morbidity associated with each depressive episode, but also the risk for chronicity, with each recurrent episode becoming more difficult to treat to full remission³⁸.

Post-hoc analyses suggested that for cognitively intact patients after remission of depression, the addition of donepezil to maintenance antidepressant pharmacotherapy appeared to have no clear benefit: it did not prevent relapse nor progression to MCI/dementia over two years. In those with MCI after remission of depression, the addition of donepezil to maintenance antidepressant pharmacotherapy appeared to prevent progression to dementia over two years but also to increase recurrence of depression. We caution, however, that these observations are based upon post-hoc subgroup analyses. The study may have been underpowered to detect a potential benefit in cognitively normal subjects. These observations are, therefore, preliminary and in need of confirmation by other studies that are designed and powered to confirm them.

There are two published, short-term pilot studies of ChEI augmentation of antidepressant treatment of non-demented older patients with major depression and cognitive impairment^{39, 40}. In a 12-week, randomized, double-blind, placebo-controlled study of 23 adults older than age 50, Pelton et al³⁹, reported that donepezil was associated with greater improvement in memory (immediate recall) than those on placebo. In a 24-week double-blind, placebo-controlled pilot study of 38 non-demented depressed adults older than 50, Holtzheimer et al.⁴⁰ observed no significant differences in measures of mood or cognition over the study 24 weeks, but did report high dropout among galantamine-randomized subjects.

While some treatment studies with ChEIs in non-demented persons with MCI have shown benefit in cognitive performance and rates of conversion to dementia^{6, 7}, others have not, for example.^{41, 42} The Cochrane review of donepezil in MCI concluded that the benefits of ChEIs are minor, short-lived, and associated with significant side effects¹³. Of interest, and consistent with our findings of a lower, slower conversion rate to dementia associated with donepezil use in MCI patients, Lu et al. study (2009)⁷ of 726 subjects with amnesic MCI randomized to donepezil, vitamin E, or placebo also found that depressive symptoms were predictive of progression from MCI to Alzheimer's Disease over three years but that donepezil slowed progression to Alzheimer's Disease relative to placebo and vitamin E. Lu et al. found that donepezil was not associated with improvement in depressive symptoms. In contrast to our study, the authors excluded subjects with episodes of major depression occurring in the previous two years, whereas we required subjects to have a current episode. Our data appear to be consistent with those of Lu et al in suggesting a lower dementia conversion rate on donepezil in MCI subjects with a history of depression. Although our data do not allow us to say whether subjects with a history of depression (as distinct from a recent episode) are at higher risk for recurrence on donepezil, such subjects should be watched carefully if placed on donepezil.

The current study differs in several respects from previously reported cholinesterase inhibitor (ChEI) trials conducted in patients with MCI: 41-44 (1) we examined older adults with major depression, a population excluded from ChEI trials, but one which is relevant to psychiatric practice with complicated older patients; (2) our study thus expands the evidence base available to treat patients that have been excluded from trials sponsored by industry and by the Alzheimer Disease Cooperative Study (ADCS) group; and (3) our study examined a more heterogeneous group of MCI subjects, including those with non-amnesic and multiple cognitive domain forms as well as the amnesic forms included in industry-sponsored and ADCS trials. Until now there has been no evidence to guide psychiatric treatment of these complicated older adults with major depression and the full spectrum of MCI.

Furthermore, in contrast to ChEI trials in dementia, where improvements in neuropsychiatric symptoms have been noted^{15, 16}, we detected a clinically significant increase in recurrent episodes of major depression. This observation may be consistent with the cholinergic hypothesis of mood disorders^{19, 20}, which holds that persons with depression show cholinergic hypersensitivity to depressogenic effects of cholinceptive agents. The observation is also consistent with a recent report of scopolamine's antidepressant efficacy in major depressive disorder.²¹ Such episodes may further amplify cognitive impairment and associated disability, thus offsetting the temporary gains in cognition observed earlier on. The positive effects of donepezil--modest cognitive and functional enhancement and slowing of dementia conversion rate-- must be weighed against the risk of recurrence of major depression in those with mild cognitive impairment and possible appearance of manic symptoms and worsening of suicidal ideation or behavior.

Unstructured Abstract (requested by Editor)

Cognitive impairment in late-life depression is a core feature of the illness. We tested whether the combination of donepezil and antidepressant pharmacotherapy (n=67) is superior to placebo + antidepressant pharmacotherapy (n=63) in improving cognition and in reducing recurrences of major depression over two years of maintenance treatment. We observed that combination donepezil + antidepressant modestly improved global cognition (including executive function, language, memory) and cognitive IADL. However, donepezil-treated patients were also more likely to experience recurrent episodes of major depression: 35% versus 19% (log rank chi squared = 3.97, p=.05).

In post-hoc analyses, we observed that of 57 participants with Mild Cognitive Impairment, three of 30 on donepezil (10%; 95% CI: 0, 21) and nine of 27 (33%; 95% CI: 16, 51) on placebo converted to dementia (primarily Alzheimer's) over two years (Fishers exact p = 0.05). However, the MCI subgroup also had a 44% recurrence rate on donepezil versus 12% on placebo (LR = 4.91, p = .03).

The cognitively normal subgroup (n = 73) showed no cognitive benefit or change in depression recurrence on donepezil.

The use of donepezil as augmentation treatment of late-life depression depends upon a careful weighing of risks and benefits in those with MCI, while no apparent benefit accrues in those with normal cognition.

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REFERENCE LIST

- (1). Nebes RD, Pollock BG, Houck PR, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: A randomized, double-blind clinical trial with nortriptyline and paroxetine. *J Psychiatr Res.* 2003; 37:99–108. [PubMed: 12842163]
- (2). Butters MA, Becker JT, Nebes RD, et al. Changes in cognitive functioning following treatment of late-life depression. *Am J Psychiatry.* 2000; 157(12):1949–54. [PubMed: 11097959]
- (3). Bhalla RK, Butters MA, Mulsant BH, et al. Persistence of neuropsychologic deficits in the remitted state of late-life depression. *Am J Geriatr Psychiatry.* 2006; 14(5):419–27. [PubMed: 16670246]
- (4). Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. *Arch Gen Psychiatry.* May; 2006 63(5):530–8. [PubMed: 16651510]
- (5). Steffens DC, McQuoid DR, Potter GG. Outcomes of older cognitively impaired individuals with current and past depression in the NCODE study. *J Geriatr Psychiatry Neurol.* March; 2009 22(1):52–61. [PubMed: 19196631]
- (6). Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology.* August 24; 2004 63(4):651–7. [PubMed: 15326237]
- (7). Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL. Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology.* June 16; 2009 72(24):2115–21. [PubMed: 19528519]
- (8). Nobili F, Vitali P, Canfora M, et al. Effects of long-term donepezil therapy on rCBF of Alzheimer's patients. *Clin Neurophysiol.* August; 2002 113(8):1241–8. [PubMed: 12140003]
- (9). Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. The “vascular depression” hypothesis. *Arch Gen Psychiatry.* 1997; 54(10):915–22. [PubMed: 9337771]
- (10). Giacobini E. Is anti-cholinesterase therapy of Alzheimer's disease delaying progression? *Aging (Milano).* June; 2001 13(3):247–54. [PubMed: 11442306]

- (11). Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc.* December; 2001 49(12):1590–9. [PubMed: 11843990]
- (12). Cummings JL. Use of cholinesterase inhibitors in clinical practice: Evidence-based recommendations. *Am J Geriatr Psychiatry.* March; 2003 11(2):131–45. [PubMed: 12611743]
- (13). Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev.* 2006; (1):5593.
- (14). Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology.* July 27; 2004 63(2):214–9. [PubMed: 15277611]
- (15). Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. *Neurology.* October; 1996 47(4):876–83. [PubMed: 8857712]
- (16). Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology.* June 27; 2000 54(12):2269–76. [PubMed: 10881251]
- (17). Howard RJ, Juszcak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med.* October 4; 2007 357(14):1382–92. [PubMed: 17914039]
- (18). Alexopoulos GS, Meyers BS, Young RC, et al. Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry.* March; 2000 57(3):285–90. [PubMed: 10711915]
- (19). Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet.* 1972; 2:632–5. [PubMed: 4116781]
- (20). Sunderland T, Tariot PN, Newhouse PA. Differential responsiveness of mood, behavior, and cognition to cholinergic agents in elderly neuropsychiatric populations. *Brain Res.* December; 1988 472(4):371–89. [PubMed: 3066441]
- (21). Drevets WC, Furey ML. Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial. *Biol Psychiatry.* 2010; 67:432–8. [PubMed: 20074703]
- (22). First, M.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P). Version 2.0 ed. New York State Psychiatric Institute; New York: 1995.
- (23). Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23:56–62. [PubMed: 14399272]
- (24). Green RC, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer disease: The MIRAGE Study. *Arch Neurol.* May; 2003 60(5):753–9. [PubMed: 12756140]
- (25). Bhalla RK, Butters MA, Becker JT, et al. Patterns of Mild Cognitive Impairment after treatment of depression in the elderly. *Am J Geriatr Psychiatry.* 2009; 17(4):308–16. [PubMed: 19307859]
- (26). Holm, MB.; Rogers, JC. The performance assessment of self-care skills (PASS). In: Hemphill-Pearson, B., editor. *Assessments in Occupational Therapy Mental Health.* 2nd ed.. SLACK; Thorofare, NJ: 2008. p. 101-10.
- (27). NACC. National Alzheimer's Coordinating Center: NACC Uniform Data Set Coding Guide. University of Washington; 2006.
- (28). Kamboh MI, Aston CE, Hamman RF. The relationship of APOE polymorphism and cholesterol levels in normoglycemic and diabetic subjects in a biethnic population from the San Luis Valley, Colorado. *Atherosclerosis.* 1995; 112:145–59. [PubMed: 7772075]
- (29). Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry.* 2004; 61:587–95. [PubMed: 15184238]
- (30). Rogers JC, Holm MB, Raina KD, et al. Disability in late-life major depression: Patterns of self-reported task abilities, task habits, and observed task performance. *Psychiatry Res.* In press 1 A.D.
- (31). Reynolds CF, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: A randomized controlled trial in patients older than 59 years. *JAMA.* 1999; 281(1):39–45. [PubMed: 9892449]
- (32). Reynolds CF, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med.* March 16; 2006 354(11):1130–8. [PubMed: 16540613]

- (33). Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*. 1958; 53:457–81.
- (34). Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81:515–26.
- (35). Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: Examples from clinical oncology data. *Journal of the American Statistical Association*. 1993; 88(422):400–9.
- (36). Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: Application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992; 41(3):237–48. [PubMed: 1594710]
- (37). Folstein MF, Folstein SW, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–98. [PubMed: 1202204]
- (38). Souery D, Oswald P, Massat I, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry*. July; 2007 68(7):1062–70. [PubMed: 17685743]
- (39). Pelton GH, Harper OL, Tabert MH, et al. Randomized double-blind placebo-controlled donepezil augmentation in antidepressant-treated elderly patients with depression and cognitive impairment: a pilot study. *Int J Geriatr Psychiatry*. July; 2008 23(7):670–6. [PubMed: 18088076]
- (40). Holtzheimer PE, Meeks TW, Kelley ME, et al. A double blind, placebo-controlled pilot study of galantamine augmentation of antidepressant treatment in older adults with major depression. *Int J Geriatr Psychiatry*. June; 2008 23(6):625–31. [PubMed: 18058832]
- (41). Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology*. May 5; 2009 72(18):1555–61. [PubMed: 19176895]
- (42). Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. June 9; 2005 352(23):2379–88. [PubMed: 15829527]
- (43). Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. *Neurology*. May 27; 2008 70(22):2024–35. [PubMed: 18322263]
- (44). Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. *Lancet Neurol*. June; 2007 6(6):501–12. [PubMed: 17509485]

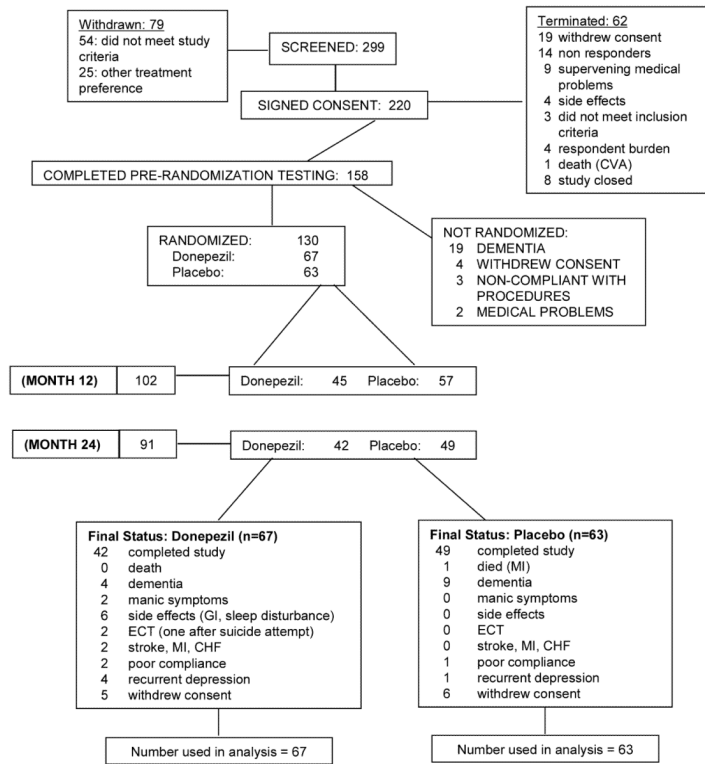


Figure 1.
Consort Flow Chart of Participants with Depression.

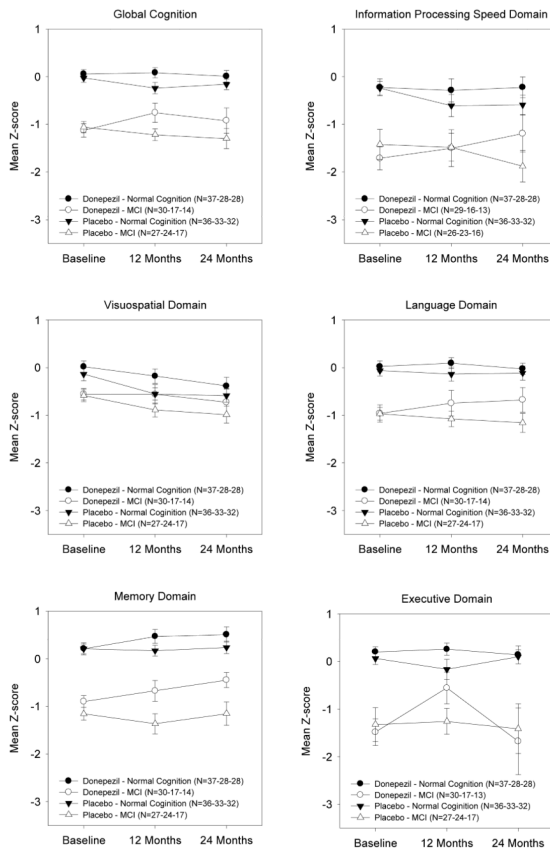


Figure 2. Donepezil + antidepressant temporarily improved global cognition relative to placebo + antidepressant (treatment x time interaction $F = 3.78$, $df = 2,126$, $p = .03$). Within specific domains, a similar treatment x time interaction was seen for executive functioning and memory. A higher-order three-way interaction was observed for language (MCI x treatment x time). Please see table 2 for mixed effects modeling results. Table 1 lists the specific neuropsychological tests that were used to compute a composite measure of global cognitive function as well as domain-specific measures

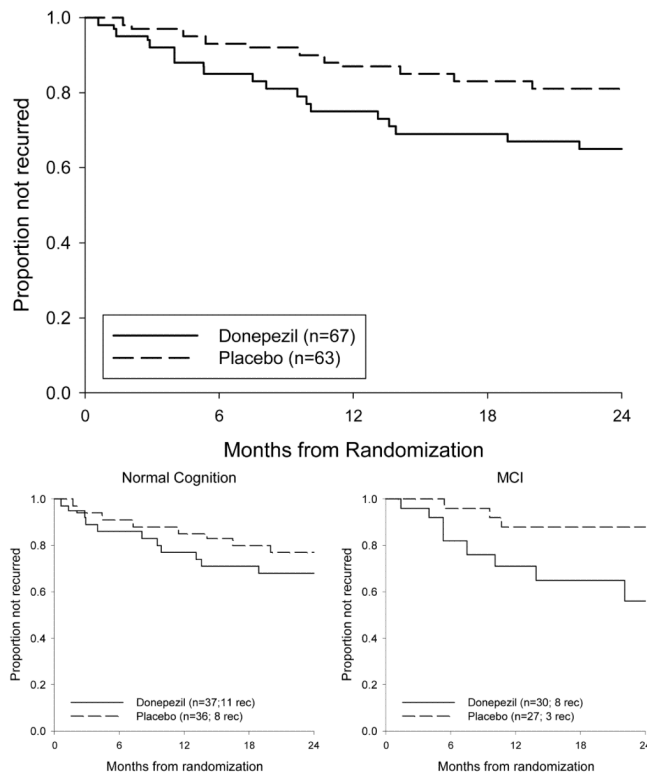


Figure 3.

The rate of recurrent major depression was 35% on donepezil versus 19% on placebo (LR=3.97, $p=.05$; number needed to harm [NNH]=6.2). Subjects with MCI had a 44% recurrence rate on donepezil versus 12% on placebo (LR=4.91, $p=.03$; number need to harm [NNH]=3.2). In subjects with normal cognition, recurrence rates did not differ on donepezil and placebo. The hazard ratio for recurrence was 4.02 (95% CI: 1.06, 15.19) in MCI subjects versus 1.49 (0.60, 3.71) in subjects with normal cognition.

Table 1

Descriptive Data N=130 Depressed

	ALL Depressed N=130	Donepezil N=67	Placebo N=63
Age	73.5 (6.2)	73.1 (6.5)	73.9 (5.8)
Gender	F=100 M=30	F=49 M=18	F=51 M=12
Education (years)	13.6 (2.5)	13.6 (2.5)	13.6 (2.6)
¹ Hamilton Depression Rating Scale @ Baseline	18.7 (3.3)	18.7 (3.3)	18.8 (3.4)
Hamilton Depression Rating Scale @ randomization	6.6 (3.2)	7.0 (3.3)	6.3 (3.1)
² Cumulative Illness Rating (CIRS-G)			
Total	10.5 (3.3)	10.5 (3.1)	10.5 (3.5)
Count	6.2 (1.9)	6.2 (2.0)	6.3 (2.0)
³ Mini-Mental State Examination (MMSE)	28.5 (1.4)	28.5 (1.4)	28.4 (1.4)
ADRC DIAGNOSIS @ randomization			
No cognitive disorder	73	37	36
MCI	57	30	27
MCI amnestic, multiple domain		14	16
MCI non-amnestic, multiple domain		8	4
MCI non-amnestic, single domain		7	4
MCI amnestic, single domain		1	3
⁴ Neuropsychological Baseline Z-scores, global cognition		-0.47 (0.88)	-0.47 (.76)
Information Processing Speed		-0.88 (1.40)	-0.74 (1.36)
Visuospatial Domain		-0.24 (0.74)	-0.33 (0.80)
Language Domain		-0.42 (0.97)	-0.45 (0.82)
Memory Domain		-0.28 (0.92)	-0.38 (0.94)
Executive Domain		-0.55 (1.40)	-0.53 (1.50)
PASS Independence			
C-IADL Observed Independence % (n)		54.1 (33/61)	61.8 (34/55)
C-IADL Self-report : Independence % (n)		48.3 (29/60)	60.0 (33/55)

Information Processing Speed: Trail Making Test A (Reitan & Wolfson, 1993), Digit Symbol Subtest (Wechsler, 1996), Grooved Pegboard (Matthews & Klove, 1964)

Visuospatial Function: Modified Rey-Osterreith Figure Copy (Osterreith, 1944; Rey, 1941), Simple Drawings (Goodglass & Kaplan, 1983), Block Design (Wechsler, 1996)

Language Function: Boston Naming Test (Goodlass & Kaplan, 1983), Spot-the-Word (Baddeley et al., 1992), Letter Fluency (Borkowski et al., 1967), Animal Fluency (Borkowski et al., 1967)

Delayed Memory: Logical Memory Delayed Recall (Wechsler, 1997), Modified Rey-Osterreith Figure Delayed Recall (Osterreith, 1944; Rey, 1941), California Verbal Learning Test Delayed Recall (Delis, 1987)

Executive Function: Stroop Neuropsychological Screening Test (Trenerry et al. 1989), Executive Interview (Royall et al., 1992), Trails Making Test B/A Ratio (Reitan & Wolfson, 1993), Wisconsin Card Sorting Test errors (Berg, 1948)

¹ Scores for the 17-item Hamilton Rating Scale for Depression range from 0-52, with higher scores indicating more severe depression.

² Scores for the Cumulative Illness Rating Scale for Geriatrics range from 0-52, with higher scores indicating worse health status.

³ Scores for the Mini-mental State Examination range from 0-30, with higher scores indicating better mental status.

⁴ Specific tests constituting our global cognitive factor (Figure 2) listed by conceptual domain

Table 2

Mixed Effects Models of Neuropsychological Performance Over Two Years

A. Global Cognition				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	1	126	0.34	0.5614
MCI	1	126	86.31	<.0001
TIME	2	126	6.36	0.0023
TREATMENT*TIME	2	126	3.78	0.0256
TIME*MCI	2	126	2.78	0.0659
TREATMENT*MCI	1	126	0.07	0.7970
TREATME*TIME*MCI	2	126	0.53	0.5900

B. Informational Processing Speed Domain				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	1	124	0.06	0.8043
MCI	1	124	34.44	<.0001
TIME	2	124	5.84	0.0038
TREATMENT*TIME	2	124	2.43	0.0923
TIME*MCI	2	124	0.63	0.5354
TREATMENT*MCI	1	124	0.59	0.4457
TREATME*TIME*MCI	2	124	1.78	0.1732

C. Visuospatial Domain				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	1	126	1.88	0.1730
MCI	1	126	12.86	0.0005
TIME	2	126	13.36	<.0001
TREATMENT*TIME	2	126	1.33	0.2694
TIME*MCI	2	126	0.42	0.6594
TREATMENT*MCI	1	126	0.09	0.7623
TREATME*TIME*MCI	2	126	0.08	0.9239

D. Language Domain				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	1	126	0.58	0.4485
MCI	1	126	43.68	<.0001
TIME	2	126	2.19	0.1156

D. Language Domain				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT*TIME	2	126	0.82	0.4443
TIME*MCI	2	126	0.95	0.3884
TREATMENT*MCI	1	126	0.29	0.5886
TREATME*TIME*MCI	2	126	3.14	0.0469

E. Memory Domain				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	1	126	5.59	0.0196
MCI	1	126	94.56	<.0001
TIME	2	126	0.85	0.4315
TREATMENT*TIME	2	126	3.93	0.0221
TIME*MCI	2	126	0.42	0.6570
TREATMENT*MCI	1	126	2.91	0.0902
TREATME*TIME*MCI	2	126	1.19	0.3089

F. Executive Domain				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	1	126	0.10	0.7517
MCI	1	126	45.99	<.0001
TIME	2	126	2.35	0.0994
TREATMENT*TIME	2	126	6.93	0.0014
TIME*MCI	2	126	4.14	0.0182
TREATMENT*MCI	1	126	0.92	0.3387
TREATME*TIME*MCI	2	126	2.00	0.1396