ORIGINAL ARTICLE

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

Objective: To test whether donepezil hydrochloride and antidepressant therapy is superior to placebo and antidepressant therapy in improving cognitive performance and instrumental activities of daily living and in reducing recurrences of depression over 2 years of maintenance treatment.

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

Setting: University clinic.

Participants: One hundred thirty older adults aged 65 years and older with recently remitted major depression.

Interventions: Random assignment to maintenance antidepressant pharmacotherapy and donepezil or to maintenance antidepressant pharmacotherapy and placebo.

Main Outcome Measures: Global neuropsychological performance, cognitive instrumental activities of daily living, and recurrent depression.

Results: Donepezil and antidepressant therapy temporarily improved global cognition (treatment × time interaction, $F_{2,126}=3.78$; $P=.03$), but effect sizes were small (Cohen $d=0.27$, group difference at 1 year). A marginal benefit to cognitive instrumental activities of daily living was also observed (treatment × time interaction, $F_{2,137}=2.94$; $P=.06$). The donepezil group was more likely than the placebo group to experience recurrent major depression (35% [95% confidence interval {CI}, 24%-46%] vs 19% [95% CI, 9%-29%], respectively; log-rank $\chi^2=3.97$; $P=.05$; hazard ratio=2.09 [95% CI, 1.00-4.41]). Post hoc subgroup analyses showed that of 57 participants with mild cognitive impairment, 3 of 30 participants (10% [95% CI, 0%-21%]) receiving donepezil and 9 of 27 participants (33% [95% CI, 16%-51%]) receiving placebo had a conversion to dementia over 2 years (Fisher exact test, $P=.05$). The mild cognitive impairment subgroup had recurrence rates of major depression of 44% with donepezil vs 12% with placebo (likelihood ratio=4.91; $P=.03$). The subgroup with normal cognition (n=73) showed no benefit with donepezil and no increase in recurrence of major depression.

Conclusions: Whether a cholinesterase inhibitor should be used as augmentation in the maintenance treatment of late-life depression depends on a careful weighing of risks and benefits in those with mild cognitive impairment. In cognitively intact patients, donepezil appears to have no clear benefit for preventing progression to mild cognitive impairment or dementia or for preventing recurrence of depression.

Trial Registration: clinicaltrials.gov Identifier: NCT00177671

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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 nondepressed subjects.[1-3] 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 2 years to improve global cognitive performance and cognitive instrumental activities of daily living (C-IADL) in older, nondemented adults with a recent major depressive episode. We chose ChEI therapy because of evidence that it may do the following: (1) prevent symptomatic progression of mild cognitive impairment (MCI),[6] especially in subjects with depressive symptoms[7]; (2) remediate cholinergic deficits and en-

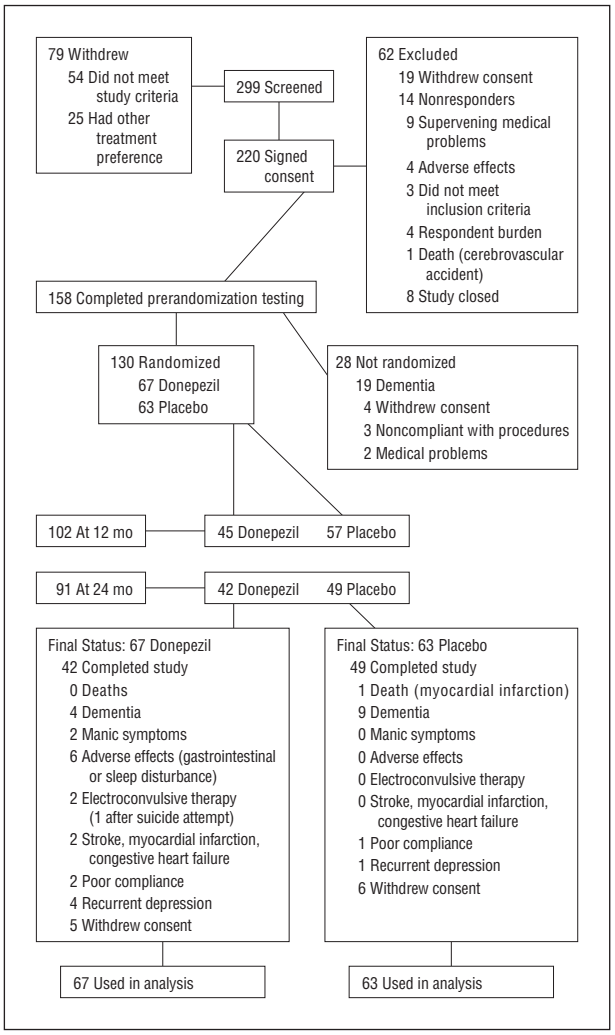

Figure 1. Randomization flowchart of participants with depression. Donepezil was given as donepezil hydrochloride.

hance cerebral blood flow—potentially an effect relevant to the pathogenesis of vascular dementia[8] and perhaps depression[9]; and (3) modify amyloid precursor protein metabolism and have neuroprotective effects.[10] In addition, we chose donepezil hydrochloride because of its potential efficacy in MCI,[6,7] pharmacokinetic properties allowing once-daily dosing, and generally good tolerability and safety data.[11] Randomized clinical trials comparing the US Food and Drug Administration–approved ChEIs in Alzheimer disease (AD) suggest no major difference in therapeutic efficacy.[12,13]

One of the most consistent effects of ChEIs in AD is the improvement of neuropsychiatric symptoms such as apathy[14-16] (but not agitation).[17] Because executive dysfunction may increase the risk of depression recurrence,[18] 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 hydrobromide produces a rapid and robust antidepressant response, possibly via modulation of *N*-methyl-D-aspartate receptor function.[21] 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 receiving maintenance antidepressant pharmacotherapy.

Our primary hypotheses were that donepezil and antidepressant therapy in older, nondemented adults with a recent major depressive episode would be superior to placebo and antidepressant therapy in the following ways: (1) improving global cognitive performance and C-IADL over a 2-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 Cochrane review's conclusions of donepezil's modest effects and adverse effect burden in MCI.[13]

METHODS

OVERVIEW

Participants received 2 phases of treatment: (1) 12 to 16 weeks of open antidepressant pharmacotherapy with supportive depression care management to bring about response and thereby to establish eligibility; and (2) the 2-year, randomized, placebo-controlled maintenance phase of treatment. Following antidepressant response during the first phase, participants had baseline neuropsychological and C-IADL assessment and adjudication of cognitive status (normal, MCI, dementia) by the University of Pittsburgh Alzheimer Disease Research Center (ADRC), Pittsburgh, Pennsylvania. Subjects were then randomized and had repeated neuropsychological and C-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 years and older from primary care practices, mental health clinics, other federally sponsored clinical research projects, and advertisements (**Figure 1**). Two hundred twenty adults qualified for participation and signed consent, 158 adults responded to open antidepressant treatment and completed assessment for the randomized controlled trial, and 130 eligible subjects agreed to randomization. The first depressed subject entered the trial in April 2004, and the last depressed subject exited the trial in September 2009.

To qualify, subjects needed to meet the following criteria: (1) be aged 65 years or older; (2) be in a nonbipolar, nonpsychotic major depressive episode[22]; (3) have a score of 15 or higher on the 17-item Hamilton Rating Scale for Depression[23]; and (4) either be cognitively normal or have 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 while receiving donepezil. We report both primary analyses of the aggregate group of all participants (N=130) and post hoc analyses of the 2 subgroups who were either cognitively normal (n=73) or were adjudicated to have MCI (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 gen-

Table 1. Descriptive Data of 130 Subjects With Depression

Characteristic	All Depressed Subjects (n=130)	Subjects Receiving Donepezil Hydrochloride (n=67)	Subjects Receiving Placebo (n=63)
Age, mean (SD), y	73.5 (6.2)	73.1 (6.5)	73.9 (5.8)
Sex, No.			
Female	100	49	51
Male	30	18	12
Education, y	13.6 (2.5)	13.6 (2.5)	13.6 (2.6)
Hamilton Rating Scale for Depression score, mean (SD)[a]			
At baseline	18.7 (3.3)	18.7 (3.3)	18.8 (3.4)
At randomization	6.6 (3.2)	7.0 (3.3)	6.3 (3.1)
Cumulative Illness Rating for Geriatrics score, mean (SD)[b]			
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)
MMSE score, mean (SD)[c]	28.5 (1.4)	28.5 (1.4)	28.4 (1.4)
ADRC diagnosis at randomization, No.			
No cognitive disorder	73	37	36
MCI	57	30	27
Amnestic, multiple domain		14	16
Nonamnestic, multiple domain		8	4
Nonamnestic, single domain		7	4
Amnestic, single domain		1	3
Neuropsychological baseline *Z* scores for global cognition, mean (SD)[d]		–0.47 (0.88)	–0.47 (0.76)
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, No./total No. analyzed (%)			
C-IADL observed independence		33/61 (54)	34/55 (62)
C-IADL self-reported independence		29/60 (48)	33/55 (60)

Abbreviations: ADRC, Alzheimer Disease Research Center; C-IADL, cognitive instrumental activities of daily living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PASS, Performance Assessment of Self-care Skills.

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

[b] Scores for the Cumulative Illness Rating Scale for Geriatrics range from 0 to 52, with higher scores indicating worse health status.

[c] Scores for the MMSE range from 0 to 30, with higher scores indicating better mental status.

[d] Specific tests constituting our global cognitive factor listed by conceptual domain are as follows: for information processing speed, we used Trail Making Test A, Digit Symbol Subtest, and Grooved Pegboard; for the visuospatial domain, we used Modified Rey-Osterreith Figure Copy, Simple Drawings, and Block Design; for the language domain, we used Boston Naming Test, Spot-the-Word, Letter Fluency, and Animal Fluency; for the delayed memory domain, we used Logical Memory Delayed Recall, Modified Rey-Osterreith Figure Delayed Recall, and California Verbal Learning Test Delayed Recall; and for the executive domain, we used Stroop Neuropsychological Screening Test, Executive Interview, Trail Making Test B/A Ratio, and Wisconsin Card Sorting Test errors.

eral, subjects had mildly to moderately severe major depression and could be safely treated as outpatients.

The ADRC consensus conference (O.L. and S.T.D.) used post-depression remission neuropsychological data, clinical history, magnetic resonance imaging data, and Performance Assessment of Self-care Skills (PASS) data.[26] The following diagnoses were made according to National Alzheimer Coordinating Center criteria[27]: no cognitive disorder, MCI amnestic–single domain, MCI amnestic–multiple domain, MCI nonamnestic–single domain, MCI nonamnestic–multiple domain, and dementia. Any participant found to be demented at baseline or to have become demented at 12 or 24 months of follow-up was removed from the study and offered open treatment with donepezil.

We tested for apolipoprotein E (*APOE*) alleles (M.I.K.) 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 the following: (1) a global measure of neuropsychological functioning; (2) a composite measure of C-IADL; and (3) recurrence of major depression.

Neuropsychological Functioning

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 nondepressed, 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 effects of donepezil and placebo on 5 domains of neuropsychological functioning: speed of information processing, executive functioning, delayed memory, language, and visuospatial functioning. 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-Osterrieth figure copy replaced clock drawing. We computed the following Cronbach α coefficients for each domain: .73 for language, .67 for visuospatial functioning, .66 for memory, .73 for executive functioning, and .79 for speed of information processing.

Cognitive 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 (eg, medication management) or physical (eg, changing bed linens) emphasis. A clinician rater observes patients perform each task and rates them according to predetermined 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 3 levels each of verbal, gestural, and physical assists. A composite measure of 13 C-IADL items included performance on activities such as shopping (cash exchange), bill paying, medication management, and home safety. Distribution of the C-IADL composite measures was dichotomous: either participants 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 Structured Clinical Interview for *DSM-IV* Axis I Disorders–Patient Edition, version 2.0 or *DSM-IV* criteria,[22] a 17-item Hamilton Rating Scale for Depression score[23] of 15 or higher over 2 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 vs primary care), cognitive status (MCI present or absent), and use of rescue medication (serotonin noradrenergic reuptake inhibitor, aripiprazole) during initial open treatment. The randomization list was prepared in advance by our statistician (S.M.). Only the research pharmacist had access to the randomization list. The blind was not broken until outcome analyses had been completed. Neuropsychological function, C-IADL, and clinical status were evaluated by independent assessors blinded to participants' randomized treatment assignment and baseline cognitive status (MCI present or absent). Identical capsules of donepezil hydrochloride (5 mg, 10 mg) and placebo were provided gratis by Pfizer Inc, New York, New York, and Eisai Inc, Woodcliff Lake, New Jersey.

INTERVENTION

To qualify for randomization to donepezil or placebo, full antidepressant response was required (defined as a Hamilton Rating Scale for Depression score ≤10 for 3 consecutive weeks). Patients initially received open antidepressant pharmacotherapy with escitalopram oxalate (≤20 mg/d). Those not responding fully were switched to a serotonin noradrenergic reuptake inhibitor (duloxetine hydrochloride, ≤120 mg/d), followed as needed by aripiprazole augmentation (≤15 mg/d) 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 more than 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 2 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 a serotonin noradrenergic reuptake inhibitor. Most of the recurrent episodes (24 of 28 recurrent episodes [86%]) were treated to response. We encouraged adherence to antidepressant pharmacotherapy at each clinic visit to ensure 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 were randomized to placebo. The mean (SD) dosage of donepezil hydrochloride at study exit was 7.8 (2.5) mg/d (mostly morning dosing), with 37 of 67 subjects receiving 10 mg/d and 30 receiving 5 mg/d (they were unable to tolerate a full dose due mainly to gastrointestinal adverse 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, University of Pittsburgh (S.A. and S.M.) and in the Department of Psychiatry, School of Medicine, University of Pittsburgh (P.R.H. and A.B.).

Primary Analysis

The primary analysis determined donepezil effects on cognition and depression recurrence in the combined group of cognitively normal participants and participants with MCI. The primary analysis of changes in outcome measures over 2 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 2-way interactions and the 3-way interaction. In the analysis of the neuropsychological measures, we used the PROC Mixed procedure. In the analysis of the dichotomized PASS data (independent vs assisted performance), we used a logistic link function in the PROC GLIMMIX procedure. All statistical analyses were conducted using SAS version 9.2 statistical software (SAS Institute, Inc, Cary, North Carolina).

We used Kaplan-Meier curves to quantify the percentage of participants who were free of depression recurrence over time.[33] Cox proportional hazard models quantified hazard ratios comparing the 2 treatment groups. Tests of proportionality were conducted via the method proposed by Grambsch and Therneau[34] and in all cases indicated that proportionality assumptions were valid. Formal tests of treatment × MCI interaction and treatment effectiveness for participants with MCI and cognitively normal participants were conducted using Cox proportional hazard 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 that adjusted for the competing causes of termination.[35] All intermittent missing values were considered missing at random.

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 C-IADL.

Post Hoc Analysis

The post hoc analysis determined donepezil effects on subgroups of cognitively normal participants and participants with MCI. We used the Fisher exact test to compare rates of dementia conversion and depression recurrence in subgroups of cognitively normal subjects (n=73) and subjects with MCI (n=57) while receiving randomized maintenance treatment with donepezil or placebo augmentation of maintenance antidepressant pharmacotherapy.

RESULTS

PRIMARY ANALYSES

Subjects receiving donepezil did not differ from those receiving placebo in age, sex, race, years of education, depression scores at baseline and randomization, medical burden (Cumulative Illness Rating Scale score),[36] cognitive status (Mini-Mental State Examination score),[37] or baseline *Z* scores for global cognition and each of the 5 domain scores (Table 1). The distribution of ADRC diagnoses (normal cognition, subtypes of MCI) also did not differ. The types of antidepressant pharmacotherapy were similar in the 2 treatment arms.

In neuropsychological performance (**Table 2** and **Figure 2**), the groups changed at different rates over time, with the donepezil group showing a temporary advantage in global cognition at 1 year that was not sustained at 2 years (treatment × time interaction, $F_{2,126}=3.78$; $P=.03$). However, group difference effect sizes were small at 1 year (Cohen $d=0.27$) and at 2 years (Cohen $d<0.05$) and were not statistically significant. Two domains of cognitive functioning demonstrated treatment × time interaction: executive function ($F_{2,126}=6.93$; $P=.001$) and memory ($F_{2,123}=3.93$; $P=.02$) (Table 2 and Figure 2). In addition, language demonstrated a higher-order interaction of treatment, time, and MCI status ($F_{2,126}=3.14$; $P=.047$).

Performance on C-IADL tasks showed a marginally different pattern of change over time in subjects receiving donepezil vs placebo (treatment × time interaction, $F_{2,137}=2.94$; $P=.06$). The percentage of subjects receiving donepezil with reported independent task performance at 12 months (Cohen $d=0.20$; $P=.27$) and at 24 months (Cohen $d=0.29$; $P=.11$) did not differ from the percentage of those receiving placebo.

We did not detect differential effects of donepezil over time on task performance observed in subjects' homes (treatment × time interaction, $F_{2,136}=0.93$; $P=.40$).

The recurrence rates of major depressive episodes (**Figure 3**) by 2 years were 35% (95% confidence interval [CI], 24%-46%) in those receiving donepezil and 19% (95% CI, 9%-29%) in those receiving placebo (log-rank test, $\chi^2=3.97$; $P=.05$; hazard ratio=2.09 [95% CI, 1.00-4.41]).

Table 2. Mixed Effects Models of Neuropsychological Performance Over 2 Years

Effect	*df*	*F* Score	*P* Value
Global cognition			
Treatment	1,126	0.34	.56
MCI	1,126	86.31	<.001
Time	2,126	6.36	.002
Treatment × time	2,126	3.78	.03
Time × MCI	2,126	2.78	.07
Treatment × MCI	1,126	0.07	.80
Treatment × time × MCI	2,126	0.53	.59
Informational processing speed domain			
Treatment	1,124	0.06	.80
MCI	1,124	34.44	<.001
Time	2,124	5.84	.004
Treatment × time	2,124	2.43	.09
Time × MCI	2,124	0.63	.54
Treatment × MCI	1,124	0.59	.45
Treatment × time × MCI	2,124	1.78	.17
Visuospatial domain			
Treatment	1,126	1.88	.17
MCI	1,126	12.86	<.001
Time	2,126	13.36	<.001
Treatment × time	2,126	1.33	.27
Time × MCI	2,126	0.42	.66
Treatment × MCI	1,126	0.09	.76
Treatment × time × MCI	2,126	0.08	.92
Language domain			
Treatment	1,126	0.58	.45
MCI	1,126	43.68	<.001
Time	2,126	2.19	.12
Treatment × time	2,126	0.82	.44
Time × MCI	2,126	0.95	.39
Treatment × MCI	1,126	0.29	.59
Treatment × time × MCI	2,126	3.14	.047
Memory domain			
Treatment	1,126	5.59	.02
MCI	1,126	94.56	<.001
Time	2,126	0.85	.43
Treatment × time	2,126	3.93	.02
Time × MCI	2,126	0.42	.66
Treatment × MCI	1,126	2.91	.09
Treatment × time × MCI	2,126	1.19	.31
Executive domain			
Treatment	1,126	0.10	.75
MCI	1,126	45.99	<.001
Time	2,126	2.35	.10
Treatment × time	2,126	6.93	.001
Time × MCI	2,126	4.14	.02
Treatment × MCI	1,126	0.92	.34
Treatment × time × MCI	2,126	2.00	.14

Abbreviation: MCI, mild cognitive impairment.

POST HOC ANALYSES OF DEMENTIA CONVERSION AND DEPRESSION RECURRENCE IN COGNITIVELY NORMAL AND MCI SUBGROUPS

Thirteen of all 130 subjects (10%) had conversion to dementia over 2 years: 1 had been cognitively normal at the start of maintenance treatment and the remaining 12 had had MCI. Thus, 12 of 57 subjects with MCI (21%) had conversion to dementia, including 3 of 30 subjects receiving donepezil (10% [95% CI, 0%-21%]) and 9 of 27 subjects receiving placebo (33% [95% CI,

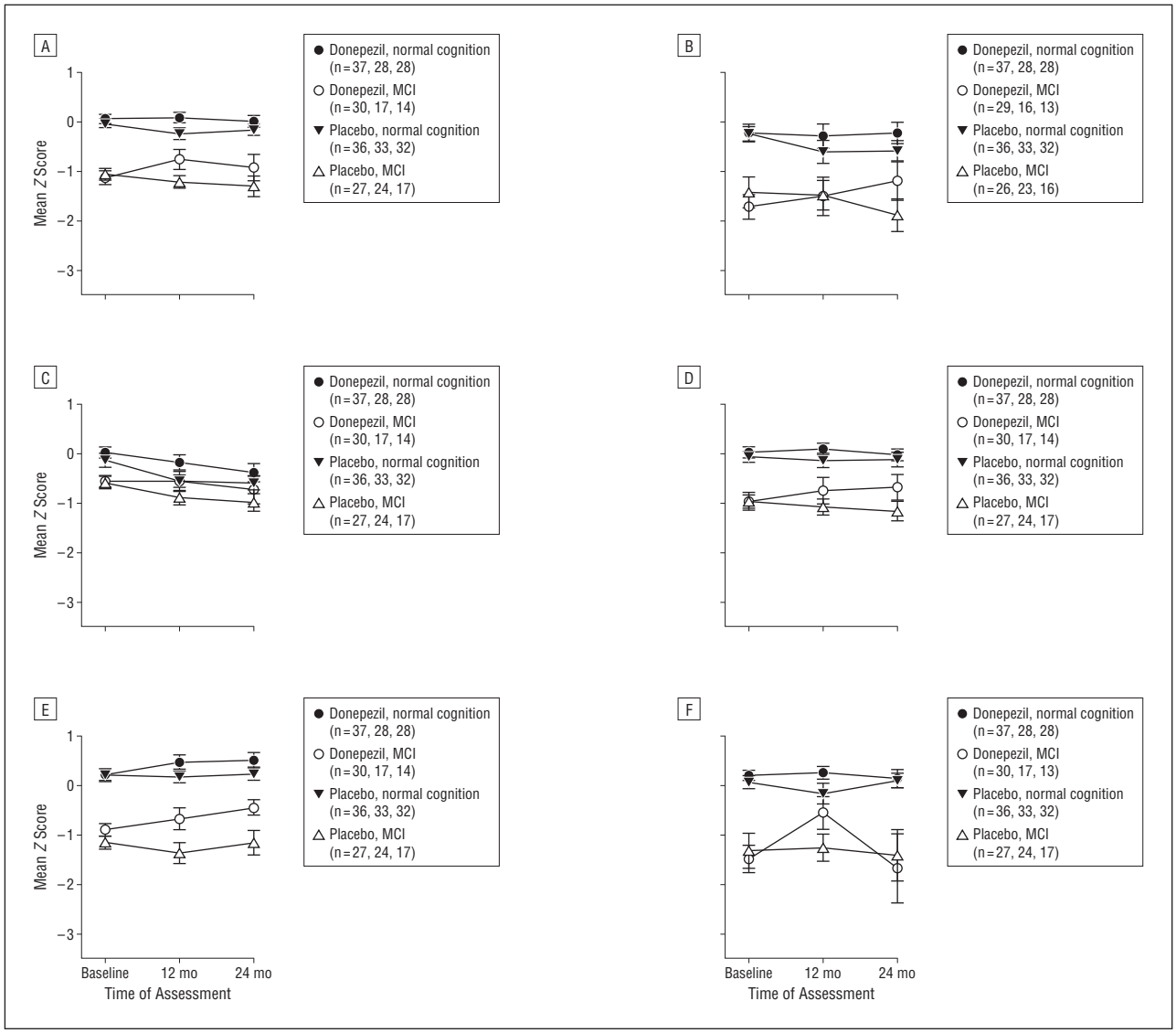

Figure 2. Neuropsychological performance over 2 years, showing global cognition (A), the information processing speed domain (B), the visuospatial domain (C), the language domain (D), the memory domain (E), and the executive domain (F). Donepezil hydrochloride and antidepressant therapy temporarily improved global cognition relative to placebo and antidepressant therapy (treatment × time interaction, $F_{2,126}$=3.78; P=.03). Within specific domains, a similar treatment × time interaction was seen for executive functioning and memory. A higher-order 3-way interaction was observed for language (mild cognitive impairment [MCI] × treatment × time). Table 2 shows 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.

16%-51%]) (Fisher exact test, P=.05). There was a trend for *APOE*4* carriers to be overrepresented among those with MCI at baseline (12 of 43 subjects) vs those with normal cognition (8 of 59 subjects) (Fisher exact test, P=.08). With respect to types of dementia adjudicated by the ADRC among 12 subjects, 8 had probable AD, 2 had possible AD, 1 had frontotemporal dementia, and 1 had other dementia. Five of 11 subjects with MCI who had *APOE* data were *APOE*4* carriers (1 carried 2/4 alleles, 4 carried 3/4 alleles). In the subgroup with normal cognition at the start of maintenance treatment (n=73), 6 of 37 subjects receiving donepezil (16%) experienced cognitive decline (5 developed MCI and 1 developed dementia), and 8 of 36 subjects receiving placebo (22%) showed cognitive decline (all MCI) (Fisher exact test, P=.56). In contrast to those showing cognitive decline, 7 of the 57 subjects with MCI at the start of maintenance treatment were adjudicated to have reverted to normal cognition on follow-up.

In the MCI subgroup, 8 of 30 subjects receiving donepezil had recurrence of major depression over 2 years vs 3 of 27 subjects receiving placebo: cumulative incidences were 44% (95% CI, 28%-60%) vs 12% (95% CI, 1%-23%) (log-rank test, χ^2=4.91; P=.03) (Figure 3). In the cognitively normal subgroup, 11 of 37 subjects receiving donepezil had recurrence vs 8 of 36 subjects receiving placebo (P=.39). Recurrence was not significantly affected by the dose of donepezil (5 mg vs 10 mg) (likelihood ratio=0.43; P=.51). Two subjects receiving 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. (Figure 1 shows a summary of adverse events associated with donepezil and placebo.)

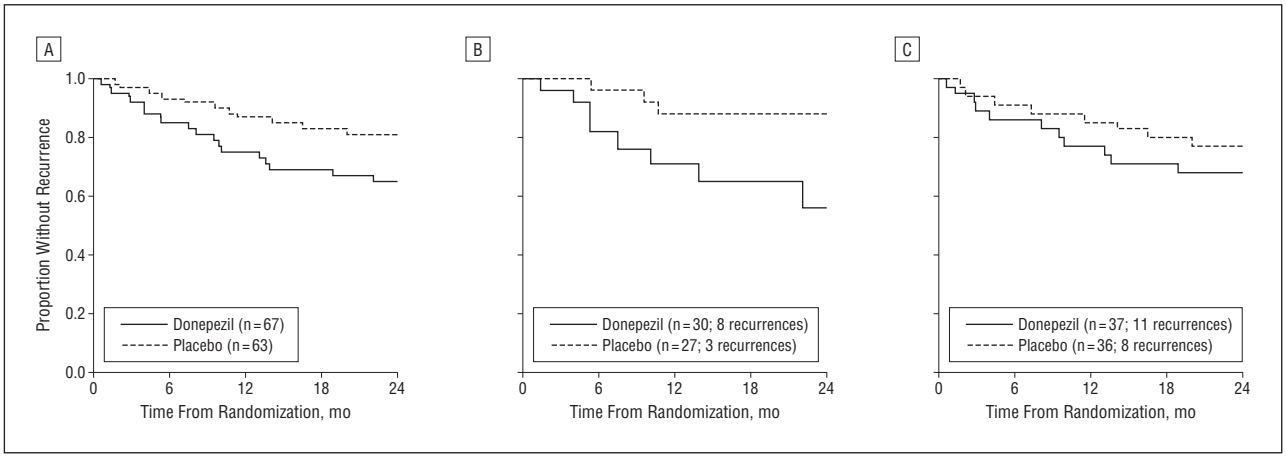

Figure 3. Recurrence of major depressive episodes. A, For all subjects, the rate of recurrent major depression was 35% when receiving donepezil hydrochloride vs 19% when receiving placebo (likelihood ratio = 3.97; $P = .05$; number needed to harm = 6.2). B, Subjects with mild cognitive impairment had a 44% recurrence rate when receiving donepezil vs 12% when receiving placebo (likelihood ratio = 4.91; $P = .03$; number needed to harm = 3.2). C, In subjects with normal cognition, recurrence rates did not differ when receiving donepezil and when receiving placebo. The hazard ratio for recurrence was 4.02 (95% confidence interval, 1.06-15.19) in subjects with mild cognitive impairment vs 1.49 (95% confidence interval, 0.60-3.71) in subjects with normal cognition.

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 (serotonin noradrenergic reuptake inhibitor, aripiprazole) following only partial response to escitalopram during phase 1. Specifically, 17 of 30 subjects who experienced recurrence (57%) vs 38 of 100 subjects who did not experience recurrence (38%) received second-line pharmacotherapy (Fisher exact test, $P = .09$). However, the proportion receiving rescue pharmacotherapy did not differ between those randomized to donepezil (29 of 67 subjects) and those randomized to placebo (26 of 63 subjects) (Fisher exact test, $P = .86$), thus suggesting that recurrence was related to the use of donepezil and not to depression treatment refractoriness. The 2 groups (with vs without recurrence) did not differ in the distribution of *APOE* alleles (Fisher exact test, $P = .21$); 19% of both those with recurrence (5 of 26 subjects) and those without recurrence (15 of 76 subjects) were *APOE*4* carriers. Subjects with amnestic and nonamnestic MCI also did not differ in the proportion experiencing recurrence of major depression (6 of 35 subjects and 5 of 22 subjects, respectively; Fisher exact test, $P = .73$). Of the 30 participants who experienced recurrence, 24 of 28 (86%) were treated to response (Hamilton Rating Scale for Depression score ≤ 10 over 3 consecutive weeks).

COMMENT

This is the first confirmatory randomized clinical trial of ChEI augmentation in older nondemented adults with a recent major depressive episode. Our primary analyses indicated 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 C-IADL, and, in a post hoc subgroup analysis of those with MCI, a lower rate of conversion to dementia over 2 years (33% in those receiving placebo vs 10% in those receiving donepezil). However, coadministration of donepezil also led to higher rates of recurrent depressive episodes than placebo (35% vs 19%, respectively, in the entire group of participants; 45% vs 12%, respectively, in the MCI subgroup) despite the use of maintenance antidepressant pharmacotherapy. The clinically significant effects of increased affective episodes are 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 remission.[38]

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 or progression to MCI or dementia over 2 years. In those with MCI after remission of depression, the addition of donepezil to maintenance antidepressant pharmacotherapy appeared to prevent progression to dementia over 2 years but also to increase recurrence of depression. We caution, however, that these observations are based on 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 2 published, short-term pilot studies of ChEI augmentation of antidepressant treatment of nondemented 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 50 years, Pelton et al[39] reported that donepezil was associated with greater improvement in memory (immediate recall) than placebo. In a 24-week, double-blind, placebo-controlled pilot study of 38 nondemented depressed adults older than 50 years, Holtzheimer et al[40] observed no significant differences in measures of mood or cognition over the study but did report high dropout among subjects randomized to galantamine hydrobromide.

While some treatment studies with ChEIs in nondemented persons with MCI have shown benefit in cogni-

tive performance and rates of conversion to dementia,[6,7] others have not.[41,42] The Cochrane review of donepezil in subjects with MCI concluded that the benefits of ChEIs are minor, short-lived, and associated with significant adverse effects.[13] Of interest and consistent with our findings of a lower, slower conversion rate to dementia associated with donepezil use in patients with MCI, a study by Lu et al[7] of 726 subjects with amnestic MCI randomized to donepezil, vitamin E, or placebo also found that depressive symptoms were predictive of progression from MCI to AD over 3 years but that donepezil slowed progression to AD relative to placebo and vitamin E. Lu and colleagues also found that donepezil was not associated with improvement in depressive symptoms. They excluded subjects with episodes of major depression occurring in the previous 2 years, whereas we required subjects to have a current episode. Our data appear to be consistent with those of Lu and colleagues in suggesting a lower rate of conversion to dementia when receiving donepezil in subjects with MCI and 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 when receiving donepezil, such subjects should be watched carefully if they begin treatment with donepezil.

This study differs in several respects from previously reported 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 that is relevant to psychiatric practice with older patients who have complicated courses; (2) our study thus expands the evidence base available to treat patients who have been excluded from trials sponsored by industry and by the Alzheimer Disease Cooperative Study group; and (3) our study examined a more heterogeneous group of subjects with MCI, including those with nonamnestic and multiple-cognitive-domain forms as well as the amnestic forms included in industry-sponsored and Alzheimer Disease Cooperative Study trials. Until now, there has been no evidence to guide psychiatric treatment of these 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 cholinoceptive 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 in treatment. The positive effects of donepezil—modest cognitive and functional enhancement and slowing of the dementia conversion rate—must be weighed against the risk of recurrence of major depression in those with MCI and possible appearance of manic symptoms and worsening of suicidal ideation or behavior.

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Author Contributions: Dr Reynolds had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Correction

Error in Text. In the Original Article titled "Neurobehavioral Abnormalities in First-Degree Relatives of Individuals With Autism" by Mosconi et al, published in the August issue of the *Archives* (2010;67[8]:830-840), an error occurred in the text. On page 835, in the first sentence of the "Predictive Saccade Task" subsection of the "Results" section, the β coefficient for the test of the group × trial interaction on saccade latencies during the predictive saccade task should have been –45.56 rather than –5.56. This article was corrected online.