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Randomized double-blind placebo-controlled donepezil augmentation in antidepressant-treated elderly patients with depression and cognitive impairment: a pilot study

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Summary

Objective—To assess combined antidepressant and cognitive enhancer treatment in elderly patients presenting with depression plus cognitive impairment.

Methods—Twenty-three elderly (>50 years old) depressed, cognitively impaired (DEP-CI) patients participated in a pilot study. We evaluated whether, after 8 weeks of open antidepressant treatment, donepezil HCl (Aricept) would afford added cognitive benefit compared to placebo in a randomized 12-week trial. A subsample continued in an 8-month extension phase of open treatment with donepezil. Neuropsychological testing (NPT) was performed and antidepressant response monitored at baseline and the 8, 20, and 52-week time points.

Results—At 8-weeks, the antidepressant response rate was 61% (14/23). Improvement in SRT immediate recall (SRT-IR; e.g. episodic verbal memory) was observed in responders compared to non-responders. During the 12-week, placebo-controlled, donepezil add-on trial, patients on donepezil showed further improvement in SRT-IR versus patients on placebo. In the open extension phase, patients who continued open donepezil treatment ($n = 6$) maintained improvement in memory and tended to show an advantage over patients who never received donepezil and were evaluated at the 52-week time point ($n = 6$). There were no observed significant donepezil effects on non-memory cognitive domains.

Conclusion—These preliminary findings suggest that addition of a cholinesterase inhibitor (AChEI) following antidepressant medication treatment in elderly Dep-CI patients may improve cognition, and support the need for a confirmatory, larger randomized placebo-controlled trial.

Keywords

depression; cognitive impairment; memory decline; donepezil; randomized clinical trial; aging

Introduction

Depression in the elderly is a major cause of suffering and disability, and worsens outcome in patients with co-morbid medical illnesses (Charney *et al.*, 2003). In the elderly, the most

common neuropsychiatric disorders are depression (DEP) and cognitive impairment (CI; e.g. defined as a transitional phase between normal and dementia). Their co-occurrence (DEP-CI) may exceed chance (Burt *et al.*, 1995). Clinical and epidemiological studies suggest that the presence of depression in patients with CI increases the likelihood of conversion to dementia, primarily Alzheimer's Disease (AD) (Devanand *et al.*, 1996; Wilson *et al.*, 2002). Therefore, treatment strategies for DEP-CI have longer-term implications beyond acute antidepressant treatment response (Alexopoulos *et al.*, 1993).

In elderly depressed patients, greater severity of depression (Yaffe *et al.*, 1999; Taylor *et al.*, 2002), increased number of prior depressive episodes (Beats *et al.*, 1996), increased age (Lyness *et al.*, 1995; King *et al.*, 1998), increased age of onset of depression (Salloway *et al.*, 1996, Rapp *et al.*, 2005), and increased vascular risk load (Hickie *et al.*, 1995; Krishnan *et al.*, 1998) appear to predict worse cognitive functioning on follow-up, but discrepant studies exist (Boone *et al.*, 1994; Butters *et al.*, 2004). In DEP-CI patients, physicians often empirically treat with antidepressant medications. Based on antidepressant response and the patient's subjective impression of cognitive improvement over time, the physician typically decides the diagnosis and treatment strategy. If cognition improves, the assumption is that the cognitive deficits are secondary to depression; if cognition does not improve, a work-up for dementia may be initiated. This approach remains to be validated by empirical research.

Extensive data support the use of acetylcholinesterase inhibitors (AChEIs), including donepezil, to treat mild to moderate AD (Burns *et al.*, 1999; Tariot *et al.*, 2000; Doraiswamy *et al.*, 2002). Some treatment studies with AChEIs targeting non-demented patient populations with CI have shown cognitive benefits though the effect size is consistently small (Christodoulou *et al.*, 2006; Demaerschalk and Wingerchuk, 2007) and the benefit may not last beyond a few months (Salloway *et al.*, 2004; Petersen *et al.*, 2005).

We previously reported limited to no improvement in cognition over a 12-week trial of open label antidepressant treatment with sertraline in 39 DEP-CI patients (Devanand *et al.*, 2003). A new DEP-CI pilot sample was recruited to evaluate the added cognitive benefit of add-on donepezil versus add-on placebo in a 12-week randomized double-blind placebo-controlled trial that took place after 8 weeks of open antidepressant treatment. A sub-sample that continued in an extension phase of open treatment with donepezil for an additional 8 months was compared to a sub-sample that was never treated with donepezil over the course of the study (see Figure 1).

Subjects and Methods

Outpatients 50 years or older were recruited from the Late Life Depression Clinic (65% of patients) and Memory Disorders Center (35% of patients) at the New York State Psychiatric Institute. These research clinics focus on depression and cognitive impairment/dementia, respectively. The study protocol was IRB-approved and written informed consent was obtained prior to study entry.

Inclusion/exclusion criteria

At baseline, the study psychiatrist (GHP or DPD) obtained a detailed medical history and conducted a general physical (including blood work), neurological, and psychiatric examination. A research social worker administered the SCID-P to evaluate Axis I disorders. Inclusion criteria for depression (DEP) were DSM-IV criteria for major depressive disorder, dysthymic disorder, or depression not otherwise specified (NOS), and a 24-item Hamilton Rating Scale for Depression (HRSD) ≥ 14 . Inclusion criteria for cognitive impairment (CI) were subjective cognitive complaints and impaired performance (> 1 SD below standardized norms on at least two tests or > 1.5 SD below standardized norms on at

least one test) on a brief neuropsychological testing (NPT) battery. No activity of daily living (ADL) deficits were allowed.

Exclusion criteria were the diagnosis of other DSM-IV Axis I psychiatric conditions, dementia, Folstein Mini Mental State (MMS) score <20/30, or identified medical or neurological cause for mood or memory impairment. Patients on antidepressants were washed out for 7 days ($n = 4$).

Outcome measures

For depression, the study psychiatrist administered the 24-item HRSD and the Clinical Global Impression scale (CGI). Side effects were assessed by the Treatment Emergent Symptom Scale (TESS). A trained technician administered the NPT battery at baseline, 8-week, 20-week, and 52-week time points. For patients who exited any phase before completion, repeat NPT was completed at the time-point of exit. The NPT battery comprised the Buschke Selective Reminding Test (targeting memory), WAIS-III digit symbol and Trails B (executive function), CFL (verbal fluency), and Trails A (attention/psychomotor speed).

Treatment trial

Phase A: Open antidepressant treatment (baseline to week 8)—Based on a pilot study (Devanand *et al.*, 2003), sertraline was the ‘first choice’ antidepressant; otherwise, ‘doctor’s choice’ was administered. Medication dose was increased in a stepwise fashion, as clinically indicated, over the first four weeks or until an optimal tradeoff between efficacy and somatic side effects were reached.

Phase B: Donepezil vs placebo (week 8 to week 20)—The 12-week randomized, double-blind, placebo-controlled, add-on donepezil phase was initiated at week-8 for all patients with persistent subjective cognitive complaints or NPT scores >1 SD below standardized norms on any test at the 8-week time-point. Donepezil or placebo (in identical-looking tablets) was dispensed at 5 mg/day for the first 4 weeks and was increased to 10 mg/day (25 mg tablets) for the remainder of the trial.

Phase C: Extended open donepezil treatment (week 20 to week 52)—After the first 20 weeks (8-weeks antidepressant + 12-weeks donepezil/placebo add-on), all patients were offered open treatment with donepezil for an additional 32 weeks with monthly monitoring. Six Phase B donepezil treated patients wanted to continue on donepezil (‘donepezil’ group), and six Phase B placebo treated patients did not wish to receive open-extension donepezil (‘no-donepezil’). This was an open, naturalistic follow-up phase.

Statistical analyses

Intent-to-Treat analyses with the Last Observation Carried Forward (ITT-LOCF) was used in each phase of the trial. A mixed ANOVA was conducted for each *a priori* defined NPT outcome measure with time (Phase A: baseline and week-8; Phase B: weeks 8 and 20; Phase C: weeks 8, 20 and 52) as the within-subjects repeated measures factor, group (Phase A: antidepressant response; Phase B: donepezil vs placebo; Phase C: donepezil vs no-donepezil) as the between-subjects factor, and group by time as the interaction effect. During Phase A, a similar ANCOVA was conducted with age and education as covariates; and during Phase B and Phase C with age, education and week 8 HRSD scores as covariates.

As defined in the data analyses plan, tests of significance were $\alpha < 0.05$ (one-tailed for all analyses), testing the hypothesis that donepezil is of therapeutic value (Ferris *et al.*, 2007).

Results

The baseline demographic, clinical and neuropsychological features of the 23 DEP-CI patients are described in Table 1. No patient had an MMSE <22, one had 22, three had 23, and the average was 26.1 with SD 2.1. 95% (22/23) of the patients met Peterson amnesic-MCI criteria (SRT-IR, and/or SRT delayed recall >1.5 SD below age and ethnicity norms (Tabert *et al.*, 2006)). Descriptive clinical and NPT results at the beginning and end of Phase B, and at the major time points in the subsample of patients included in the combined Phase B + C, are presented in Table 2.

Phase A: Open antidepressant treatment (baseline to week-8)

At 8 weeks, the antidepressant response rate was 61% (14/23) in the intent-to-treat sample and 67% (14/21) among completers. Baseline HRSD and NPT scores did not differ between responders and non-responders ($p > 0.40$).

Mixed ANOVA revealed a significant group (antidepressant responder vs. non-responder) by time interaction for SRT-IR ($F = 4.42$, $p = 0.02$), with responders showing an improvement. When age and education were included as covariates, the interaction remained significant ($F = 3.3$, $p = 0.045$).

There were no significant responder/non-responder effects on the NPT measures in the non-memory domains ($p > 0.10$).

Phase B: Donepezil vs placebo (week-8 to week-20)

In the week-8 to week-20 randomized, double-blind placebo-controlled trial, 12 patients received donepezil and nine patients received placebo. Week-8 age, HRSD, TESS and NPT scores did not differ between patients randomized to donepezil and placebo ($p > 0.10$).

In mixed ANOVA, there was a trend-level group (donepezil vs placebo) by time interaction for SRT-IR ($F = 3.0$, $p = 0.05$). Patients on donepezil tended to show an improvement in SRT-IR ($t = 1.69$, $p = 0.05$) in contrast to patients on placebo ($t = 0.80$, $p = 0.23$). When age and education, or age, education, and week-8 HRSD scores were included as covariates, the interaction did not demonstrably change ($F = 3.3$, $p = 0.04$; $F = 2.9$, $p = 0.06$, respectively).

There were no group by time effects (p -values > 0.50) on any non-memory domain measures (see Table 2 for means). Baseline MMSE did not correlate with change in performance on any NPT measures. The effect size, using Cohen's standardized mean difference (d) for the Group by Time interaction, (calculated by using the mean SRT-IR difference scores [20 - 8 week] for the donepezil and Placebo groups and dividing by the pooled standard deviation), and total SRT-IR as the dependent variable, was 0.78, which is considered in the medium to large range.

Combined Phases B + C: Extended open donepezil treatment (week-8 to week-52)

Week-8 mean HRSD score was significantly lower in the donepezil ($n = 6$) vs no-donepezil ($n = 6$) group ($p = 0.04$), but NPT scores did not differ ($p > 0.10$).

In mixed ANOVA, there was a significant group (donepezil/no-donepezil) by time interaction for SRT-IR ($F = 3.3$, $p = 0.03$). Post-hoc simple within-group effects revealed a significant effect for donepezil over time ($F = 4.1$, $p = 0.03$) but not for the no-donepezil group ($F = 0.44$, $p = 0.3$) (Figure 2). When age and education, or age, education, and week-8 HRSD scores were included as covariates, the interaction remained significant ($F = 5.2$, $p < 0.01$; $F = 5.2$, $p < 0.01$, respectively).

There were no group by time effects (i -values > 0.20) on any non-memory domain measures (see Table 2 for means).

Somatic side effects

Donepezil treated patients reported the same level of side effects as the placebo treated patients in total TESS scores during Phase B (donepezil mean = 3.2 SD = 3.3 vs placebo mean = 3.2, SD = 3.2); and during Phase C (donepezil mean = 2.5 SD = 2.6 vs no-donepezil mean = 1.8, SD = 1.9).

Discussion

In this pilot study, elderly DEP-CI patients treated with an antidepressant plus donepezil had a short-term improvement in verbal memory compared to treatment with antidepressant plus placebo. This effect waned in patients who continued in open donepezil treatment for an additional 8 months. The time course and magnitude of improvement with donepezil are consistent with donepezil treatment studies of MCI (Petersen *et al.*, 2005) and AD (Rogers *et al.*, 1998), where measurable cognitive improvement was observed in the first few months, followed by a plateau or gradual decline.

Improvement limited to the memory domain is consistent with past AChEI studies in AD, which demonstrated benefits in memory more commonly than other domains (Burns *et al.*, 1999). In studies of MCI patients, donepezil has shown superiority over placebo in the attention/psychomotor (Salloway *et al.*, 2004), executive (Saykin *et al.*, 2004) and language (Petersen, 2005) domains, but these findings have been inconsistent. The small sample size and large variance within the donepezil and placebo groups may account for our negative findings in non-memory domains. In addition, even though we had a placebo-control arm to address practice effects in Phase-B, a learning effect may also account for our negative findings in non-memory domains.

While our findings must be interpreted with caution, given the small sample size and limited length of follow-up, the cognitive improvement observed in this DEP-CI sample indirectly suggests that donepezil treatment is well tolerated and may delay cognitive decline and conversion to AD, an outcome of clear clinical value (Devanand *et al.*, 1996; Petersen *et al.*, 2001; Tabert *et al.*, 2006). These pilot data also suggest that the cognitive benefit conferred to DEP-CI patients by AChEI treatment may be at least as substantial as that previously reported for CI patients without depression (Salloway *et al.*, 2004; Petersen *et al.*, 2005). Also, given the high prevalence of depression in the context of late-life CI, including depressed patients in future AChEI treatment trials for MCI and AD could increase the generalizability of such trials.

A limitation includes the heterogeneous inclusion criteria for depression, including depressions of varying severity and duration. A distinction within subgroups of depression (e.g. major depression vs dysthymia) may reveal significant differences in treatment response to an AChEI. However, small sample size precludes these analyses.

In the elderly DEP-CI patient, the beneficial effects of donepezil indirectly suggest that cholinergic neurotransmitter deficits contribute to the CI associated with DEP, similarly to MCI (Gron *et al.*, 2006) and AD (Davis *et al.*, 1985). Since deficits in the catecholamine neurotransmitter system (e.g. norepinephrine and serotonin) are also known to be associated with depression and to modulate cognitive performance (e.g. executive function; Schmitt *et al.*, 2006), the cognitive improvements with combination antidepressant plus donepezil may involve independent but overlapping neurotransmitter systems.

In summary, the results of this pilot study raise the possibility that combined treatment with anti-depressant and AChEI may be considered in patients presenting with DEP-CI. It also provides a basis for a larger study that, if successful, may represent a possible approach to reducing conversion rates to a clinical diagnosis of dementia.

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Figure 1.

Flow diagram of patient treatment stratification during the trial.

* 2 patients dropped during Phase A and thus were excluded from Phase B analysis.

** 6 patients who had been assigned to donepezil during Phase B chose not to continue donepezil treatment during Phase C and thus were excluded from the Phases B + C analysis.

*** 3 patients who had been assigned to placebo during Phase B chose to begin donepezil treatment during Phase C and thus were excluded from the Phases B + C analysis.

Figure 2.
Change in SRT Immediate recall during the donepezil vs no-donepezil treatment.

Table 1
Baseline demographic and clinical features and neuropsychological raw scores of patients with depression and cognitive complaints ($n = 23$)

Baseline features	Mean (SD) or %
Age (years)	67.7 (8.7)
Sex (% female)	56.5%
Education (years)	13.3 (4.5)
<i>Ethnicity*</i>	
White non-Hispanic	56.5%
African-American non-Hispanic	21.7%
Hispanic	17.4%
Other	4.3%
Diagnosis of Major Depressive Disorder	78.0%
24-item HRSD	22.2 (4.2)
Age at first depression (years)	53.8 (19.4)
Duration of depression (months)	30.4 (35.3)
Duration of memory complaints (months)	37.2 (34.2)
Family history of dementia	9.0%
Family history of depression	48.0%
30-item Folstein MMSE	26.1 (2.1)
Selective Reminding Test Immediate Recall	33.4 (9.5)
Verbal Fluency (CFL)	36.7 (16.6)
WAIS-III Digit Symbol	41.8 (20.4)
Trails A (seconds)	78.8 (34.0)
Trails B (seconds)	190.5 (95.1)

* At baseline, ethnicity was documented by self-report.

Table 2
Raw scores in clinical and neuropsychological measures in subjects included in Phase B and Phases B + C analyses

<i>Measure</i>	Phase B: week 8–week 20 Donepezil vs placebo			Combined phases B + C: week 8–week 52 Donepezil vs. no donepezil			
	Donepezil (<i>n</i> = 12) Vs. Plac. (<i>n</i> = 9)	Pre-drug Mean (SD)	Post-drug Mean (SD)	Donepezil (<i>n</i> = 6) No Don. (<i>n</i> = 6)	Week 8 Mean (SD)	Week 20 Mean (SD)	Week 52 Mean (SD)
<i>Clinical</i>							
24-item HRSD	Donepezil	9.3 (7.1)	10.4 (8.1)	Donepezil	6.2 (3.3)	6.0 (2.5)	6.2 (2.6)
	Placebo	7.8 (3.9)	4.6 (2.9)	No Don.	13.5 (8.1)	13.0 (10.1)	10.3 (8.5)
TESS total intensity	Donepezil	4.3 (4.0)	3.2 (3.3)	Donepezil	2.8 (3.3)	2.8 (2.3)	2.5 (2.6)
	Placebo	3.4 (4.0)	3.2 (3.2)	No Don.	6.0 (3.3)	3.5 (3.5)	1.8 (1.9)
<i>Neuropsychological</i>							
<i>Verbal memory</i>							
SRT Immediate Recall	Donepezil	32.8 (11.9)	37.8 (10.9)	Donepezil	31.7 (7.7)	41.7 (9.5)	35.3 (3.6)
	Placebo	41.0 (13.6)	39.0 (12.0)	No Don.	36.5 (15.3)	36.3 (12.9)	35.0 (11.4)
<i>Verbal fluency</i>							
CFL	Donepezil	35.3 (15.0)	35.8 (15.1)	Donepezil	37.0 (12.9)	39.2 (13.8)	35.0 (11.9)
	Placebo	40.0 (15.3)	42.4 (17.9)	No Don.	36.8 (9.8)	33.2 (10.6)	34.8 (13.5)
<i>Attention/psychomotor</i>							
Trails A	Donepezil	69.1 (26.3)	60.2 (19.8)	Donepezil	76.5 (28.6)	64.8 (19.2)	61.7 (20.1)
	Placebo	103.0 (64.6)	96.0 (47.6)	No Don.	87.8 (67.3)	77.3 (30.4)	72.7 (46.3)
<i>Executive</i>							
Trails B	Donepezil	183.5 (98.0)	198.0 (95.1)	Donepezil	178.3 (103.0)	170.7 (108.7)	175.2 (100.6)
	Placebo	201.0 (96.3)	177.0 (89.9)	No Don.	190.8 (99.8)	195.6 (96.4)	128.5 (16.5)
WAIS-III digit symbol	Donepezil	46.0 (21.1)	46.8 (20.2)	Donepezil	43.8 (22.5)	46.3 (16.8)	42.3 (17.5)
	Placebo	36.0 (20.6)	39.0 (22.8)	No Don.	42.7 (18.9)	35.0 (17.6)	38.0 (18.2)