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Sertraline treatment of elderly patients with depression and cognitive impairment

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SUMMARY

Background There is little information on the efficacy and side effects of antidepressant treatment in elderly patients with combined depression and cognitive impairment without dementia (DEP-MCI), and it is unclear if cognitive performance improves with antidepressant response in these patients.

Methods In 39 elderly DEP-MCI patients, changes in depression and cognitive impairment were evaluated with open sertraline treatment up to 200 mg/day for 12 weeks.

Results Of the 26 completers, 17 were responders and nine were non-responders. Diagnostic subtype of depression was unrelated to response. ANCOVA on WAIS-R digit symbol percent change scores revealed a significant effect for responder status ($F = 5.59, p < 0.03$), and age ($F = 0.24, p < 0.64$) and education ($F = 1.64, p < 0.22$) were not significant covariates. From pre-trial to post-trial, responders improved in WAIS-R digit symbol percent change scores (Mean -10% SD 24) while non-responders declined (Mean 14% SD 18; $t = 2.60, p < 0.02$). Other neuropsychological measures were unrelated to response. Percent change in HRSD scores showed significant inverse correlations with percent change in several cognitive measures.

Conclusions DEP-MCI patients showed moderate clinical response to sertraline treatment. When responders were compared to non-responders, cognitive improvement was limited to one measure of attention and executive function. Overall, there was little cognitive improvement with antidepressant treatment. The findings indirectly suggest that lack of improvement in cognition following treatment of depression in DEP-MCI patients may be associated with increased risk of meeting diagnostic criteria for dementia during follow-up. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — depression; cognition; attention; memory; executive function; sertraline; dementia; Alzheimer's disease

The most common late-life neuropsychiatric disorders are depression and dementia, with both identified as major public health problems that will grow rapidly with the aging population in the 21st century

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(Alexopoulos *et al.*, 1993a; Devanand *et al.*, 1996). Epidemiological studies report a 10 to 35% prevalence of depressive symptoms in the elderly (Blazer *et al.*, 1987; Devanand *et al.*, 1996; Bassuk *et al.*, 1998), and a 10 to 40% prevalence of cognitive impairment that increases markedly with age (Coria *et al.*, 1993; Hanninen *et al.*, 1995; Koivisto *et al.*, 1995). As the elderly population increases, the proportion of patients with concurrent depression (DEP) and mild cognitive impairment (MCI; Peterson *et al.*, 1995), defined broadly in this paper to include subjects between 'normal' and 'dementia', will also increase. Depressive and cognitive disorders frequently co-exist in elderly patients (Boone *et al.*, 1992; Kindermann and Brown,

1997) and the association between DEP and MCI, or DEP and dementia, may go beyond chance (Burt *et al.*, 1995; Henderson *et al.*, 1997). Clinical (Alexopoulos *et al.*, 1993a) and epidemiologic (Devanand *et al.*, 1996; Bassuk *et al.*, 1998) studies suggest that the presence of depression (DEP) increases the risk of dementia in patients with mild cognitive deficits, with few dissenting reports (Chen *et al.*, 1999).

Neuropsychological test profiles typically differ between patients with depression and mild dementia. Patients with early dementia, primarily Alzheimer's disease (AD), have delayed word recall test deficits (Coen *et al.*, 1997), verbal learning task deficits (Delis *et al.*, 1992), and language deficits (Hill *et al.*, 1992). In contrast, the memory impairments in depression seem to be secondary to deficits in attention and motivation (Weingartner *et al.*, 1983). Most studies in patients with MDD (Burt *et al.*, 1995), including geriatric MDD (Kindermann and Brown, 1997), have reported a robust and consistent decrease in task performance in the areas of speed of information processing, motor functioning, and executive function (Boone, 1995; Kindermann and Brown, 1997).

Attention, psychomotor and executive function deficits can be severely impaired during depression, and are likely to reverse with remission of depression (La Rue *et al.*, 1986; Reynolds *et al.*, 1987). In contrast, memory deficits are mild to moderate in severity and typically are believed not to reverse with remission of depression (Cohen *et al.*, 1982; Sternberg and Jarvik, 1986). Clinical trials using tricyclic antidepressants (TCAs) or electroconvulsive therapy (ECT) in elderly patients with major depression (MDD) suggest that cognitive deficits often improve along with recovery from depression (Reynolds *et al.*, 1987; Sackeim *et al.*, 1993). However, in DEP-MCI patients, it is not known which cognitive deficits reverse after effective antidepressant treatment, or whether patients who have persistent cognitive deficits after treatment are likely to develop dementia. The clinical bias has been to treat the depression first and if cognitive impairment persists, then complete a neuropsychiatric work-up for dementia (Rabins *et al.*, 1984; Emery and Oxman, 1992). These clinical views have not been tested systematically in treatment trials in DEP-MCI patients.

We conducted an open 12-week trial of antidepressant treatment with sertraline, with neuropsychological testing conducted before and after the trial. The hypotheses were that performance on tests of attention and executive function would improve to a greater extent in responders compared to non-responders to sertraline treatment, but changes in

memory and language performance would not be associated with treatment response.

SUBJECTS AND METHODS

Outpatients 50 years of age or older were recruited from two sources at the New York State Psychiatric Institute: Memory Disorders Clinic (54% of patients) and Late Life Depression Clinic (46% of patients). These clinics specialize in conducting clinical research studies in outpatients with cognitive impairment/dementia and geriatric depression, respectively. The Memory Disorders Clinic recruited patients primarily through physician referral and the Life Depression Clinic recruited patients primarily through advertising.

The study protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute. All patients provided written informed consent.

Inclusion/exclusion criteria

All patients met inclusion criteria for depression and cognitive impairment without dementia. Inclusion criteria for depression were the presence of depressed mood or lack of interest for ≥ 2 consecutive weeks and a 17-item Hamilton Rating Scale for Depression (HRSD) ≥ 8 . Patients who met DSM-IV criteria for major depressive disorder, dysthymic disorder, or depression NOS (not otherwise specified) were included. Exclusion criteria were the presence of any contraindication to sertraline, lack of response in the current depressive episode to a minimum six-week trial of an SSRI at an adequate dose (fluoxetine ≥ 40 mg/day, sertraline ≥ 150 mg/day, paroxetine ≥ 40 mg/day, or citalopram ≥ 40 mg/day), active suicidal ideation or plan, psychotherapy (any type) at a frequency greater than once/month, diagnosis of dementia, stroke (clinically manifest), major neurological disorders, alcohol or substance abuse or dependence in the past six months, bipolar disorder, schizophrenia or other psychotic disorder, and severe unstable medical conditions.

Inclusion criteria for cognitive impairment were the presence of intellectual impairment for ≥ 6 months and ≤ 10 years, and impaired neuropsychological test performance (>1 SD below standardized norms) on at least one test from a brief neuropsychological battery: WAIS-R digit span, digit symbol and similarities subtests, 15-item subtest of the Boston Naming test, animal naming and CFL (verbal fluency), Selective Reminding Test (SRT; delayed recall), and two cancellation tasks (letter and shape; time to complete these tasks). Exclusion criteria were

a Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) score <17 out of 30 or a clinical diagnosis of dementia based on a consensus conference.

At initial evaluation, the study psychiatrist obtained a detailed medical history and conducted a general physical, neurological, and psychiatric examination. Electrocardiogram, and blood work including complete blood count, electrolytes, liver and renal functions, and thyroid functions were completed prior to study entry. Brain CT or MRI scan was done when indicated.

Depression evaluations

A research social worker administered the SCID-P at baseline to evaluate Axis I disorders. The study psychiatrist administered the 17-item Hamilton Rating Scale for Depression (HRSD) and the Clinical Global Impression (CGI) at each study visit. On the HRSD, inter-rater reliability was established in 20 patients between the raters with an intraclass correlation coefficient of 0.95. The patient completed the Beck Depression Inventory II self-report at each visit. The study psychiatrist (D.P.D. or G.H.P.) conducted clinical management based on standard therapeutic principles in antidepressant clinical trials, and completed side effect ratings using the Treatment Emergent Symptom Scale (TESS) that was modified for SSRI side effects by adding items for sexual dysfunction and restlessness/jitteriness.

Cognition evaluations

A trained technician administered the brief neuropsychological test battery at the start and end of the trial. These tests were chosen because they tap into areas (attention, memory, language, abstract reasoning, executive function) that are known to be affected in MCI and in depressive disorders.

Other measures

Age of onset of depressive illness (current and first-ever episode), and age of onset of cognitive impairment, were determined by evaluation of all medical records, interviewing the patient, and interviewing an informant when available (Alexopoulos *et al.*, 1993b). The modified Blessed Functional Activity Scale (Parts I and II) was used to assess activities of daily life (Blessed *et al.*, 1968; Stern *et al.*, 1990).

Treatment trial

The minimum pre-study washout for psychotropic medications was seven days. Putative antidepressants

such as St John's wort also required a seven-day washout. Other medications not known to interact adversely with sertraline were not changed during the study. During the trial, lorazepam equivalents up to 2 mg/day were permitted to treat anxiety/insomnia.

In this 12-week trial, patients were evaluated at one-week intervals for the first two weeks and subsequently at two-week intervals. Patients started sertraline (A.M. dose) at 50 mg/day for the first week. In the absence of intolerable side effects, the dose was raised to 100 mg/day. At the end of week 4, if the patient did not meet criteria for response in the absence of intolerable side effects, the dose was raised to 150 mg/day for the next four weeks, and to 200 mg/day for the final four weeks in the absence of clinical response or intolerable side effects. At any time-point in the trial, if the patient met response criteria that dose was continued for the rest of the trial unless subsequent loss of clinical response or incident side effects required further change in dosage.

Both the following criteria needed to be met for antidepressant treatment response: CGI (assessing depression only) score of 1 (not at all ill) or 2 (borderline mentally ill) on the study psychiatrist's evaluation, and $\geq 50\%$ decline in HRSD scores from baseline.

At eight weeks into the treatment trial, blood levels for sertraline and desmethyl sertraline levels were drawn 12–24 hours post-oral dose.

Statistical analyses

In descriptive statistics, the results for continuous variables are expressed as mean (SD), and as percentages for categorical variables. All statistical tests were two-tailed.

For patients who exited the protocol before completion, repeat neuropsychological testing was not completed at the point of exit. Therefore, intent-to-treat analyses with the last observation carried forward could not be conducted in this trial, and the main analyses were completer analyses. ANCOVAs were conducted separately on the percent change in each of the neuropsychological measures from pre- to post-trial, with responder status as the between subject factor and age and education as covariates. Following the ANCOVAs, *post hoc t*-tests were used to evaluate differences between responders and non-responders. Pearson correlation coefficients were used to evaluate the associations between percent change in HRSD scores and the neuropsychological measures. Student's *t*-test was used to compare responders and non-responders on the percent change

Table 1. Demographic and clinical features of 39 patients with depression and cognitive impairment

Baseline features	Mean (SD) or %
Age in years	72.0 (10.2)
Sex (% female)	64.1%
Education in years	12.0 (4.8)
Duration of memory complaints in months	33.5 (24.4)
Duration of depressive complaints in months	24.4 (20.6)
Family history of depression	22%
Family history of dementia	36.5%
Self-referred (includes brought in by informant)	73.7%
Age first depressed in years	63.9 (16.6)
Current major depression	53.8%
History of major depression	33.3%
17-item HRSD	15.4 (4.5)
Folstein MMSE score	25.7 (3.8)
CGI illness severity (range 1 to 7)	3.4 (0.5)
CIRS-G (number of medical illnesses)	3.7 (2.2)

MMSE = Mini-Mental State Examination range 0–30; CGI = Clinical Global Impression; CIRS-G = Cumulative Illness Rating Scale-Geriatric.

in TESS scores. The criterion for significance was $\alpha = 0.05$.

RESULTS

The demographic and clinical features of the 39 patients are described in Table 1. The ethnic distribution was 66.7% non-Hispanic white, 28.2% Hispanic and 5.1% African-American. Memory complaints were the first symptom in 46.2% of patients, depression was the first symptom in 35.9% of patients, and the chronological sequence of these two symptoms was unclear in 17.9% of patients. Memory decline was reported as more disturbing by 28.2%, depression as more disturbing by 48.7%, and both as equally disturbing by 23.1%. In the index episode, 56.4% of patients had not received any treatment for depression, 38.5% had received antidepressant medication, 2.6% had received psychotherapy, and 2.6% had received combined medication and psychotherapy. Most patients (84.6%) were not taking putative cognitive enhancers; 2.6% were taking cholinesterase inhibitors, 5.1% were taking vitamin E, 5.1% were taking ginkgo biloba and 5.1% were taking more than one such medication. These putative cognitive enhancers were kept constant in dosage throughout the treatment trial.

Efficacy and cognitive change

Twenty-six of the 39 study participants completed the trial. Reasons for early protocol exit were acute gas-

trointestinal distress ($n = 3$), anorgasmia ($n = 1$), other somatic side effects ($n = 2$), increase in anxiety ($n = 2$), withdrawal of consent ($n = 1$), moving residence ($n = 1$), and other reasons ($n = 3$).

Of the 26 completers, 17 were responders and nine were non-responders. Response was unrelated to subtype of depression (major depression $n = 13$ vs rest of sample $n = 13$; $\chi^2 = 0.2$, $p < 0.7$) and percent change in Blessed Functional Activity Scores ($t = 0.7$, $p < 0.5$). Responders were younger (Mean 66.8 years, SD 9.4) than non-responders (Mean 82.3 years, SD 5.0; $t = 4.6$, $p < 0.001$). Age showed a significant inverse correlation with baseline scores on SRT delayed recall ($r = -0.40$, $p < 0.05$), but not with the other neuropsychological measures. Age of onset of depressive symptoms and age of onset of cognitive impairment were unrelated to treatment response. The type of first symptom (depression or cognitive impairment) and the more subjectively distressing symptom (depression or cognitive impairment) were unrelated to treatment response ($\chi^2 = 4.3$, $p < 0.12$ and $\chi^2 = 2.0$, $p < 0.4$, respectively). Sex was unrelated to responder status and to all neuropsychological test scores (baseline, or percent change from pre-trial to post-trial). Education in years was unrelated to response ($t = 0.6$, $p < 0.6$), but showed significant correlations with baseline scores on WAIS-R similarities ($r = 0.63$, $p < 0.001$), WAIS-R digit symbol ($r = 0.57$, $p < 0.05$), and verbal fluency (CFL $r = 0.40$, $p < 0.05$; animal naming $r = 0.45$, $p < 0.03$), but not with the other neuropsychological measures. Based on these associations, only age and education were included as covariates in the analyses.

Separate ANCOVAs were conducted on the percent change in each of the neuropsychological measures from pre- to post-trial, with responder status as the between-subject factor and age and education as covariates (Table 2). In these analyses, responder effects were observed only on WAIS-R digit symbol scores. ANCOVA on percent change in WAIS-R digit symbol scores revealed a significant effect for response ($F_{3,23} = 5.59$, $p < 0.03$), and age ($F_{3,23} = 0.24$, $p < 0.64$) and education ($F_{3,23} = 1.64$, $p < 0.22$) were not significant covariates. Responders improved in WAIS-R digit symbol percent change scores (Mean -10% SD 24) while non-responders declined (Mean 14% SD 18; $t = 2.60$, $p < 0.02$). Among the 17 responders, seven showed $>10\%$ improvement, three showed $>10\%$ decline and seven did not change (improve or decline by more than 10%) in WAIS-R digit symbol scores. Among the nine non-responders, none showed $>10\%$ improvement, five showed $>10\%$ decline and four did not change (improve or

Table 2. ANCOVAs on neuropsychological measures (% change scores) with response (17 responders, nine non-responders) as between subject factor, and age and education as covariates

Dependent variable	Between subject, covariates	F	p <
Folstein MMSE	Responder	0.65	0.43
	Age	4.73	0.05
	Education	0.10	0.76
Digit span	Responder	0.06	0.80
	Age	0.43	0.52
	Education	3.82	0.07
SRT total recall	Responder	0.0	0.99
	Age	2.15	0.16
	Education	1.42	0.25
SRT delayed recall	Responder	1.01	0.33
	Age	0.01	0.92
	Education	0.03	0.86
Verbal fluency CFL	Responder	0.46	0.51
	Age	0.72	0.41
	Education	0.38	0.55
Animal naming	Responder	1.71	0.21
	Age	0.60	0.45
	Education	3.41	0.08
Boston naming	Responder	2.37	0.14
	Age	0.01	0.92
	Education	0.51	0.48
WAIS-R similarities	Responder	0.07	0.80
	Age	0.68	0.42
	Education	1.06	0.31
WAIS-R digit symbol	Responder	5.59	0.03
	Age	0.24	0.64
	Education	1.64	0.22
Letter cancellation time	Responder	0.41	0.54
	Age	2.13	0.55
	Education	1.26	0.28
Shape cancellation time	Responder	1.60	0.22
	Age	4.73	0.05
	Education	0.40	0.54

decline by more than 10%) in WAIS-R digit symbol scores (Table 3).

Percent change in HRSD scores showed a trend-level inverse correlation with percent change in MMS ($r = -0.38, p < 0.06$), and significant inverse correlations with percent change in SRT total recall ($r = -0.44, p < 0.03$), percent change in WAIS-R digit symbol ($r = -0.53, p < 0.01$), and percent change in time to complete a letter cancellation task ($r = -0.51, p < 0.01$), but not with the other neuropsychological measures.

Somatic side effects

Responders reported significantly less side effects than non-responders in percent change in total TESS scores (responders Mean 30% SD 30 vs non-responders Mean -10%, SD 30, $t = 3.3, p < 0.005$).

Oral dose and blood levels

The mean end-point sertraline oral dose did not differ between responders (Mean 144.1 SD 52.7 mg/day) and non-responders (Mean 147.2 SD 40.4 mg/day; $t = 0.15, p < 0.9$). Sertraline blood levels tended to be higher in responders (Mean 84.8 ng/ml SD 59.5) compared to non-responders (Mean 43.8 ng/ml SD 23.4; $t = 1.96, p < 0.07$), and desmethyl sertraline levels tended to be higher in responders (Mean 108.5 ng/ml SD 48.7) compared to non-responders (Mean 72.6 ng/ml SD 35.8; $t = 1.98, p < 0.07$).

Table 3. Neuropsychological test scores in responders ($n = 17$) and non-responders ($n = 9$) pre-trial and end-trial

Neuropsychological measure	Responders				Non-responders			
	Pre-trial		End-trial		Pre-trial		End-trial	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Folstein Mini-Mental State Examination	25.7	3.3	26.4	3.0	25.7	3.8	24.7	3.0
Digit span (forward + back)	8.8	1.3	8.5	1.5	9.1	1.4	9.0	1.7
SRT total recall	38.3	11.1	38.4	13.5	35.8	7.6	30.8	6.9
SRT delayed recall	4.4	3.2	4.9	2.8	3.4	2.1	3.7	1.7
Verbal fluency CFL	29.0	14.9	31.3	11.6	34.4	12.5	39.0	14.7
Animal naming	12.8	4.6	14.5	4.1	13.0	3.2	12.6	5.0
Boston naming test: 15-item	13.5	1.5	13.4	2.0	13.4	2.1	14.2	1.6
WAIS-R similarities	13.2	7.7	14.2	6.3	16.4	5.9	15.3	6.5
WAIS-R digit symbol	30.7	12.4	33.2	13.9	28.2	9.5	25.3	11.2
Letter cancellation time	89.7	29.4	85.4	35.4	88.6	27.7	91.6	73.5
Shape cancellation time	68.5	22.7	70.2	30.3	71.2	20.5	78.4	36.6

MMSE = Mini-Mental State Examination; SRT = Selective Reminding Test of Buschke and Fuld; WAIS = Wechsler Adult Intelligence Scale.

DISCUSSION

Patients with DEP-MCI showed moderate antidepressant response to open treatment with sertraline for 12 weeks. These results suggest that sertraline represents a viable treatment option in DEP-MCI patients, and are consistent with the literature on antidepressant treatment of depressed elderly patients with and without cognitive impairment (Sternberg and Jarvik, 1976; Reynolds *et al.*, 1987; Nyth *et al.*, 1992). There is evidence that sertraline treatment is associated with a small improvement in cognition in normal elderly volunteers, but practice effects could not be ruled out in that report (Furlan *et al.*, 2001).

In this study, responders to sertraline improved more on the WAIS-R digit symbol subtest than non-responders. This test primarily assesses attention and executive function. However, percent change in the WAIS-R digit span, which is a test of attention, did not differ between responders and non-responders. Therefore, the findings with measures of attention in these DEP-MCI patients are only partly consistent with prior studies involving successful treatment of depression (Kindermann and Brown, 1997; Newhouse *et al.*, 2000). There were no significant differences on the other neuropsychological measures, including measures of memory. The lack of association between treatment response and changes in measures of memory is consistent with most of the literature on cognitive changes with treatment response in major depression (Kindermann and Brown, 1997). Percent change in HRSD scores showed significant inverse correlations with some neuropsychological measures of psychomotor speed, executive function, memory, and global cognitive performance, indicating that improvement in depression (lower HRSD scores) was associated with improvement in neuropsychological test performance in these areas, as has been reported in studies of depressed patients (Boone *et al.*, 1992; Kindermann and Brown, 1997).

Given the short interval of 12 weeks between neuropsychological testing sessions, practice effects should have led to some improvement in cognitive performance regardless of antidepressant treatment. The observed lack of change, or worsening, in cognitive performance in several patients is of concern. This outcome raises the possibility that DEP-MCI is a high risk group for further cognitive decline or progression to dementia and, if so, there is a need to identify which patients will become demented. Studies in patients with DEP-MCI or similar disorders suggest that there is a two-to-five fold increased risk of conversion to a clinical diagnosis of dementia, primarily

AD, during follow-up (Alexopoulos *et al.*, 1993a; Devanand *et al.*, 1996; Bassuk *et al.*, 1998).

Although there is a lack of published treatment trials evaluating changes in cognition with antidepressant treatment in DEP-MCI patients, this issue has been examined in treatment trials of depression in AD patients. In a multi-center, double-blind placebo-controlled trial using moclobemide (a reversible monoamine oxidase inhibitor) in 511 patients with DEP and AD, there was a significant reduction in depression scores in 60% of moclobemide treated patients and 49% of placebo patients. Global cognitive functioning, as measured by the MMSE, improved significantly more on moclobemide than placebo (Roth *et al.*, 1996). In a double-blind, placebo-controlled trial in 149 patients, citalopram significantly reduced depression scores in 45% of patients compared to 24% for placebo (Nyth *et al.*, 1992). On the Gottfries-Brane-Steen dementia rating scale (GBS; Gottfries *et al.*, 1982), cognitive and emotional functioning improved significantly more on citalopram compared to placebo. In contrast, in a double-blind placebo-controlled trial of imipramine in AD patients with major depression, Reifler *et al.* (1989) found no change in MMSE in either group. In another double-blind study of 21 subjects with probable AD and depression, clomipramine was superior to placebo, with no significant differences on change in MMSE (Petraffa *et al.*, 1996). Katona *et al.* (1998) found comparable antidepressant efficacy for imipramine and paroxetine in patients with depression and probable AD, but no change in cognition in the two groups. Overall, these controlled trials showed that improvement in global cognitive tests was either absent or small in magnitude in patients with AD and concurrent depression after effective antidepressant treatment. Our findings in DEP-MCI patients suggest a similar outcome, in that neuropsychological test scores did not improve in most non-responders, and even in some responders (Table 3). These findings raise the possibility that a large proportion of these patients may decline cognitively to meet diagnostic criteria for dementia, primarily AD, during follow-up.

The limitations of this study were the small sample size and lack of availability of neuropsychological testing at the time-point of dropout. As a result, the statistical analyses were restricted to completer analyses. Nonetheless, the findings do provide useful pointers for the clinician: DEP-MCI patients show moderate clinical response with sertraline treatment, and cognitive performance in the domains of attention and executive function can improve with antidepressant treatment. However, in patients whose cognition

does not improve with antidepressant treatment of depression, there may be an increased risk of meeting criteria for dementia during follow-up. Longitudinal follow-up studies after systematic treatment of DEP-MCI patients are needed to address this issue.

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