Cognitive Effects of Paroxetine in Older Depressed Patients

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This study examined whether paroxetine produces cognitive toxicity in elderly patients suffering from a major depressive episode. Twenty-nine depressed patients with a wide range of cognitive functioning were treated with paroxetine. At baseline and during 6 weeks of treatment, patients were asked to complete various measures of cognitive function and had blood drawn to determine serum anticholinergicity. Measures of attention and cognitive speed showed significant improvement with treatment, while the memory performance remained unchanged. A similar pattern of results was found in both cognitively impaired and intact patients. The slight increase in serum anticholinergicity seen in some elderly patients did not significantly impair cognitive function, even in patients with a preexisting cognitive impairment.
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Selective serotonin reuptake inhibitors (SSRIs) are generally considered especially appropriate for treating geriatric depression because they lack the significant anticholinergic effects of the tricyclic antidepressants. The loss of central nervous system cholinergic function that occurs with increasing age leads to an increased incidence of disruptive anticholinergic side effects, such as sedation and cognitive deficits, in older depressed patients prescribed one of the tricyclics.[1–3] However, data from an in vitro radioreceptor assay[4] suggest that paroxetine, an SSRI often used to treat geriatric depression, is almost as potent a muscarinic antagonist as imipramine. Although Pollock and colleagues,[5] using an in vivo assay of serum anticholinergicity (SA),[6] found that paroxetine had only one fifth the anticholinergic potential of nortriptyline in geriatric depressed patients, paroxetine still produced a detectable increase in SA. Because the elderly are very sensitive to anticholinergic medications,[7] even the low levels of anticholinergicity associated with paroxetine treatment might be sufficient to produce significant cognitive decrements in older patients. For example, Nebes et al. found that even the very low levels of SA present in some older patients prior to antidepressant treatment were associated with significant memory deficits.[8] Thus, it is important to test directly whether paroxetine produces any cognitive toxicity in older depressed patients, especially because such patients often present with preexisting cognitive impairments that may make them even more sensitive to anticholinergic side effects.

Few studies have examined the cognitive effects of paroxetine, especially in the depressed elderly, and these have used either behavioral rating scales, such as the Sandoz Clinical Assessment Geriatric scale, or screening instruments, such as the Mini-Mental State Examination (MMSE),[9,10] that are not particularly sensitive to the types of memory and information-processing deficits associated with anticholinergic medications. Therefore, the present study examined cognitive change in geriatric depressed patients during acute treatment with paroxetine. Because many elderly depressed patients have some degree of cognitive impairment, we believed that it was important to include patients with mild-to-moderate cognitive deficits in this study to determine whether such individuals might be disproportionately sensitive to any cognitive toxicity associated with paroxetine. This sample of depressed patients is thus more cognitively impaired than those found in many treatment studies of elderly depressed patients and even includes some patients carrying a presumptive diagnosis of dementia.

METHOD

We tested 29 elderly patients experiencing a major depressive episode (nonpsychotic, nonbipolar) recruited from

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2 geriatric inpatient units (N = 11) and the outpatient late-life depression clinic (N = 18) of the Western Psychiatric Institute and Clinic, a teaching hospital of the University of Pittsburgh Medical Center. After the patients had signed an informed consent statement, they received a comprehensive evaluation[11] by a geropsychiatric team. This included the MMSE,[12] the Dementia Rating Scale (DRS),[13] the Structured Clinical Interview for DSM-IV Disorders,[14] and the Hamilton Rating Scale for Depression (HAM-D),[15] as well as a social and medical history. The patients also received a physical examination and a battery of laboratory tests. Based on all available information, consensus Axis I and Axis II diagnoses were made according to DSM-IV[16] criteria during a diagnostic consensus conference. For entry into the study, a patient's baseline HAM-D (17 item) score had to be above 15. The HAM-D scores ranged between 16 and 31 (mean ± SD = 20.9 ± 3.7). The patients were between 61 and 84 years of age (mean ± SD = 70.7 ± 6.4 years) and had 7 to 18 years of education (mean ± SD = 11.6 ± 3.0). DRS scores at baseline ranged between 115 and 144 (mean ± SD = 132.6 ± 9.1), where 144 is the maximum score. Ten of the 29 patients scored less than 131 on the DRS prior to treatment and thus could be considered cognitively impaired.[17]

All of the patients were participating in a larger double-blind randomized trial comparing long-term treatment with nortriptyline or paroxetine.[18] Random assignment to 1 of the 2 medications was stratified according to inpatient versus outpatient status and cognitive status (baseline MMSE ≤ 24 vs. > 24). The patients included in the present report had completed 6 weeks of treatment with paroxetine. The initial dose was 10 mg/day for outpatients and 20 mg/day for inpatients. The dose typically was increased to 20 mg/day for all patients after 1 week and, in the absence of improvement, to a maximum of 40 mg/day. By week 6, 2 patients were taking 10 mg/day, 19 patients were taking 20 mg/day, 6 patients were taking 30 mg/day, and 2 were taking 40 mg/day. Patients were reassessed weekly with the HAM-D and other scales. Cognitive testing occurred at baseline and at 1, 4, and 6 weeks after beginning treatment with paroxetine.

The patients were administered a variety of cognitive measures known to be sensitive to depression and anticholinergic medications. The first was the Trail Making Test (Trails), which has 2 parts. Part A measures the time subjects take to connect consecutively a series of 25 numbered circles scattered about a page. Part B measures how long they take to connect consecutively numbered and lettered circles, alternating between letters and numbers (i.e., 1, A, 2, B, 3, etc.). Although both parts make a substantial demand on visual search and motor speed, part B also requires subjects to shift sets between digits and numbers while keeping track of their place in the sequence of both.

The second task was the Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Test-Revised.[19] In this task, a code table at the top of the page contains the digits 1 through 9 arranged in numerical order. Below each digit in the table is a different symbol. Under the code table are rows of double boxes, one box above the other. In the top of each double box is a digit, while the bottom box is empty. The subject has 90 seconds to write in each bottom box the symbol that is paired with that digit in the code table. The DSST has been shown to be an excellent measure of information processing speed.[20]

Subjects were also given a copy task, which has the same general format as the DSST with the exception that the digits above the response boxes are replaced by the symbols associated with those digits in the coding key. All the subject has to do is to copy the symbols, so motor requirements of the copy task are the same as the DSST, but the cognitive demands are substantially less.[21]

The next task was a verbal learning test, in which participants heard a list of 15 common unrelated words presented at the rate of 1 word per second and had to recall immediately as many words as possible in any order. They received 4 presentations of the same word list, the words being given in a different order on each presentation. After their fourth immediate recall of the list, there was a 30-minute interval during which the subjects performed other nonverbal tasks. This was followed by a delayed recall test without further presentation of the word list. From this verbal learning test we obtained 3 measures: (1) the total number of words recalled across the 4 immediate recall trials, (2) delayed recall, and (3) percent retention, which is equal to the delayed recall score as a percentage of a subject's recall score on the last immediate recall trial. For example, if the subject had recalled 10 of the words on the fourth immediate recall trial and only 3 words on delayed recall, the percent retention was 30%. Different lists of words equated for difficulty were used in each of the 4 testing sessions.

Before each of the 4 cognitive testing sessions, a 10-mL blood sample was drawn to determine each patient's SA. The serum was stored at –20° C until assayed. We applied a radioreceptor binding assay developed by Tune and Coyle[6] that uses the specific binding of tritiated quinuclidinyl benzilate (3H-QNB) for rat muscarinic brain receptors from the striatum and forebrain to quantify the concentration of anticholinergic drugs in the serum. Anticholinergic drugs competitively inhibit binding of 3H-QNB to rat muscarinic receptors. Atropine was used for displacement at various concentrations, and the results are reported in picomoles of atropine equivalents.

RESULTS

We carried out a series of independent repeated-measures analyses of variance (ANOVAs) comparing the test scores at the 4 time points using a mixed effects proce-

Table 1. The Effect of Treatment With Paroxetine on Cognitive Performance, Covaried for Baseline Performance on the Dementia Rating Scale (DRS)[a]

	Effect of Treatment[b]			Interaction With Baseline DRS Score		
Measure	F	df	p Value	F	df	p Value
Trails A	5.5	3,80	< .002	3.0	3,80	< .04
Trails B	4.5	3,80	< .006	0.5	3,80	NS
DSST	16.2	3,75	< .0001	0.3	3,75	NS
Copy task	16.5	3,75	< .0001	0.4	3,75	NS
Total recall	1.4	3,81	NS	0.2	3,81	NS
Delayed recall	0.6	3,81	NS	0.4	3,81	NS
% Retention	1.0	3,81	NS	2.2	3,81	NS

[a]Abbreviations: DSST = Digit Symbol Substitution Test, Trails = Trail Making Test.
[b]Baseline measures vs. week 6 measures.

Table 2. The Effect of Treatment With Paroxetine on Cognitive Performance After Covarying for Serum Anticholinergicity

	Effect of Treatment			Interaction With Baseline DRS Score		
Measure	F	df	p Value	F	df	p Value
Trails A	6.1	3,79	< .001	3.3	3,79	< .03
Trails B	6.3	3,79	< .001	0.7	3,79	NS
DSST	15.9	3,74	< .0001	0.4	3,74	NS
Copy task	18.3	3,74	< .0001	0.3	3,74	NS
Total recall	1.3	3,80	NS	0.2	3,80	NS
Delayed recall	0.7	3,80	NS	0.4	3,80	NS
% Retention	0.9	3,80	NS	2.4	3,81	NS

dure.[22] All analyses were run using the baseline DRS scores as a continuous covariate along with a treatment interaction term. This allowed us to determine whether any treatment effects on the various tasks interacted with the patients' baseline level of cognitive functioning. That is, did the cognitive effects of paroxetine vary with the degree of cognitive impairment present in the depressed patients prior to their treatment? The results for Trails A and B (time to complete each task) were highly skewed, so they were transformed using a natural logarithm. None of the other results required a transformation. The DSST and copy tasks were added to the test battery after the study was underway, so data on these tests were not available for 3 patients.

The HAM-D scores decreased significantly ($F = 121.4$, $df = 3,81$; $p < .0001$) across the treatment period, falling from a mean ± SD of 20.9 ± 3.7 to 9.4 ± 4.3, with 20 of the 29 patients scoring below 10 by week 6. Baseline DRS scores did not interact with this reduction in HAM-D scores ($F = 1.5$, $df = 3,81$), indicating that the antidepressant effect of paroxetine did not vary as a function of the patients' cognitive status at baseline. Trails A and B, the DSST, and copy tasks all showed a significant improvement across the 6 weeks of treatment (Table 1). None of the memory measures, however, showed any significant change, although delayed recall and percent retention did decline slightly, especially within the first week of treatment. As might be expected, the baseline DRS score was significantly related to all cognitive test measures (except the copy task) in that the patients with lower DRS scores performed more poorly than did those with higher DRS scores (Trails A: $F = 11.5$, $df = 1,27$; $p < .003$; Trails B: $F = 25.8$, $df = 1,27$; $p < .0001$; DSST: $F = 9.7$, $df = 25$, $p < .01$; total recall: $F = 16.2$, $df = 1,7$; $p < .001$; delayed recall: $F = 19.7$, $df = 1,27$; $p < .0001$). However, baseline DRS score did not interact with the treatment effect for any of the cognitive tasks except Trails A (Table 1). This single significant interaction was driven by the results of one demented patient (DRS = 115), who showed a dramatic improvement in Trails A score from baseline to week 1. If the results of this one patient were removed, the interaction was no longer significant. Thus, the severity of the patients' preexisting cognitive impairment did not affect the change in cognitive performance that accompanied treatment with paroxetine. Overall, this initial analysis did not produce any evidence that paroxetine causes a substantial decrement in cognitive performance in this elderly depressed sample, even in the cognitively impaired patients. If anything, the patients' performance improved on several of the measures. When we carried out the same analysis on just the 20 patients who had responded to treatment by the end of 6 weeks, the pattern of results was essentially unchanged.

It is possible, however, that paroxetine produces anticholinergic effects only in certain patients and that just these individuals will show a cognitive decrement with treatment. Looking at the group as a whole, the increase in mean SA over the 6 weeks was not significant ($t = 1.99$, $df = 28$), rising from 0.08 to 0.16 pmol/L. Twelve patients showed no change in SA from baseline to week 6, while 5 experienced a small decline. Twelve patients did show a rise in SA, but in only 7 of these was the increase in excess of 0.1 pmol/L. To examine the effect that changes in SA had on cognitive performance, we reran the previous analyses incorporating SA as a covariate. Covarying for the effect of change in SA with treatment had minimal effect on the magnitude of the treatment effect or the interaction between treatment and baseline DRS scores (Table 2). Thus, there was no evidence that the small changes in SA that occurred with paroxetine treatment influenced the pattern of cognitive performance associated with paroxetine treatment. Some studies have found that demented patients are more sensitive than nondemented elderly patients to anticholinergic medications.[23] However, in the present study, we found no evidence that changes in SA had a differentially greater effect on cognitively impaired patients (i.e., those with lower DRS scores).

DISCUSSION

In this study, acute treatment with paroxetine was not associated with any cognitive impairment in geriatric patients being treated for a major depression. Instead, there

was an actual improvement on several timed tasks, although memory performance remained unchanged. This pattern of results was not affected by the cognitive status of the depressed patients at baseline. Even cognitively impaired patients showed improvement in their performance on the timed tasks. This cognitive improvement over the course of treatment could result either from the decreased level of depression seen in most of the patients or from a practice effect that comes from performing the same task multiple times. We are presently testing a series of nondepressed elderly controls at the same timepoints to determine whether the improvement in the depressed patients' performance is any greater than would be expected from practice. However, regardless of the source of the improvement in these patients, it is clear that their cognitive performance did not deteriorate from acute treatment with paroxetine, even if the patients had a preexisting cognitive impairment.

Studies on the cognitive effects of antidepressant treatment in geriatric patients have yielded inconsistent results. Some studies, especially those using tricyclic antidepressants, have shown an actual decrement,[2,24] or at best, no change.[25] Other studies, especially those using SSRIs, have found some evidence for an improvement in cognitive functioning.[9,10,24] There is also little information available on the interaction of treatment with preexisting cognitive impairment. One study found that cognitively intact patients showed an improvement in performance following treatment with nortriptyline, a secondary tricyclic antidepressant, while cognitively impaired patients did not change.[3] Another study found that depressed patients with Alzheimer's disease actually experienced some cognitive decrement when treated with imipramine, a tertiary tricyclic antidepressant.[26] This is in contrast to the findings in the present study, in which the cognitive improvement found with treatment with an SSRI was similar in cognitively impaired and cognitively intact patients. It is possible that the nature of the antidepressant (i.e., tricyclic vs. SSRI) may greatly influence whether cognitively impaired, and especially demented, patients show cognitive improvement with treatment of their depression.

There was a slight increase in SA with paroxetine treatment in a subgroup of depressed patients. However, changes in SA with treatment did not appear to influence cognitive performance, even in patients who were cognitively impaired prior to treatment. That is, there was no evidence that depressed patients who were cognitively impaired were any more sensitive to this slight rise in SA than were those who were intact. Thus, while treatment with paroxetine can be associated with some increase in SA in some geriatric patients, this increase does not appear to lead to any significant cognitive decrements, even in patients with a presumptive diagnosis of dementia.

Drug names: nortriptyline (Pamelor and others), paroxetine (Paxil).

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