Pilot Study of Haloperidol, Fluoxetine, and Placebo for Agitation in Alzheimer's Disease

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This pilot study compared haloperidol, fluoxetine, and placebo for reduction of agitation in 15 outpatients with AD. The two drugs were no more effective than placebo at reducing agitation in these subjects; however, both drugs produced more toxicity than did placebo.

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Agitated behaviors in patients with Alzheimer's disease (AD) produce significant physical and emotional stress for both patients and caregivers[1] and are more likely to prompt institutionalization than are physical infirmities or incontinence.[2] Despite these facts, there are surprisingly few appropriately designed clinical trials comparing different treatments for this common neuropsychiatric problem.[3]

Abnormalities in serotonergic function are well recognized in AD.[4,5] Decreased platelet ^{3}H-imipramine binding density has been demonstrated in agitated compared with nonagitated AD patients.[6] Similarly, greater reductions in cortical serotonin binding sites have been described in AD patients with hallucinations compared with nonpsychotic AD patients.[7] Consequently, we hypothesized that a selective serotonin reuptake inhibitor (SSRI) might prove useful in the treatment of agitated patients with AD. Published clinical data also support the use of SSRIs to treat behavioral problems in demented patients.[8] Thus, the purpose of this exploratory pilot study was to conduct a randomized, double-blind, placebo-controlled, parallel group–design clinical trial comparing the efficacy and toxicity of a typical neuroleptic (haloperidol), an SSRI (fluoxetine), and placebo for reducing agitation in outpatients with AD.

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METHODS

Fifteen community-dwelling outpatients meeting NINCDS-ADRDA criteria[9] for probable or possible AD who showed disruptive agitated behaviors and who scored ≥ 25 on the short form Cohen-Mansfield Agitation Inventory[10] (CMAI) were enrolled in this study. Patients with a history of schizophrenia, schizoaffective disorder, or Parkinson's disease were excluded, as were patients who currently met DSM-III-R criteria for major depressive episode or for manic episode. Each subject received a diagnostic evaluation, including medical and neuropsychiatric history, physical examination, and laboratory screening, before undergoing random, double-blind assignment to one of three parallel treatment groups (n = 6 in each group).

Subjects in each group completed a 2-week washout period during which any current psychotropic medications were carefully withdrawn. The three groups then entered a 6-week fixed-dose active treatment period where one group received haloperidol (3 mg every morning), one group received fluoxetine (20 mg every morning), and one group received daily placebo medication. The research protocol and informed consent forms were approved by our local institutional review board. After complete description of the study to the subjects and caregivers, written informed consent was obtained from both parties.

The primary outcome measure was the CMAI.[10] Secondary outcome measures included the sum of scores on sections C, D, and E of the Behavioral Pathology in Alzheimer's Disease Rating Scale[11] (BEHAVE-AD) and total score on the University of Iowa Caregiver Stress Inventory (CSI). Each outcome measure was administered to the primary caregiver after the 2-week washout period (baseline), after 3 weeks of active treatment, and after 6 weeks of active treatment (endpoint). Toxicity was measured by the total number of adverse symptoms occurring throughout the protocol as recorded on a standardized questionnaire constructed specifically for this study and administered at each evaluation. The adverse

symptoms investigated by this questionnaire included specific changes in alertness, mobility, and mood, as well as more general symptoms such as changes in weight or gastrointestinal function.

Efficacy of treatment on each outcome measure was compared by use of a repeated-measures analysis of variance model (treatment × time interaction; baseline versus endpoint). Bonferroni's correction was applied to account for the effect of multiple comparisons. Outcome data from subjects who did not complete the full 6 weeks of active treatment were managed according to "intent-to-treat" analysis techniques (last observation carried forward).[12] Toxicity in each group was compared by one-way analysis of variance with the Fisher protected least significant difference test used for post hoc comparisons. For subjects who did not complete all 6 weeks of active treatment, the number of adverse symptoms (at endpoint) was determined by linear extrapolation of the subject's available toxicity data.

RESULTS

Subjects' mean age (± SD) was 75.6 ± 7.5 years. The subjects included 10 women and 5 men. Mean educational level was 12.1 ± 5.4 years, mean duration of dementia (assessed by caregiver report) was 3.7 ± 1.9 years, and mean Mini-Mental State Examination[13] (MMSE) score was 15.2 ± 4.6. The three groups did not differ significantly from one another in age, gender, education, duration of dementia, or severity of dementia (as measured by MMSE). Similarly, the three groups did not differ significantly from one another on baseline scores for any of the three outcome measures. Nine subjects were receiving no psychotropic medications prior to the washout period, 3 were receiving trazodone, 2 were receiving a neuroleptic, and 1 was receiving both a neuroleptic and a benzodiazepine. There was no difference among the three groups in the percentage of subjects who had been receiving psychotropics prior to the washout period.

All 15 subjects completed the 2-week washout period and the first 3 weeks of active treatment without difficulty. However, in 3 subjects, treatment-associated toxicity led to termination of study participation between the fourth and sixth weeks of active treatment. Two of these 3 subjects were receiving haloperidol, and the third was receiving placebo. Parkinsonism and oversedation were the reasons for early termination in the 2 haloperidol-treated subjects; parkinsonism and akathisia were the reasons for early termination in the subject receiving placebo.

Subjects' baseline scores on the CMAI ranged from 25 to 44, with a mean score of 35.2 ± 5.5. Endpoint CMAI scores ranged from 17 to 45, with a mean score of 34.4 ± 8.4. None of the three treatments was superior to the others at reducing CMAI scores ($F = 0.21$, df = 2,12, $P = 0.82$). Similarly, there was no difference in the effects of the three treatments on BEHAVE-AD scores ($F = 1.16$, df = 2,12, $P = 0.35$) or on CSI scores ($F = 0.41$, df = 2,12, $P = 0.67$).

The mean number of adverse symptoms was 15.6 ± 2.4 in the haloperidol-treated group, 15.4 ± 5.0 in the fluoxetine-treated group, and 7.3 ± 7.6 in the placebo group. These group means were significantly different from one another ($F = 3.82$, df = 2,12, $P = 0.05$), the placebo group demonstrating significantly fewer adverse symptoms than either the haloperidol or the fluoxetine group. The most common adverse symptoms recorded in the haloperidol-treated group were depression of mood, anxiety/nervousness, and difficulty walking. In the fluoxetine-treated group and in the placebo group, the most commonly recorded adverse symptoms were anxiety/nervousness, worsening of confusion, and tremor. Efficacy and toxicity data are summarized in Table 1.

DISCUSSION

The treatment of agitation in dementia and AD is a major clinical problem in geriatric neuropsychiatry. Physicians often attempt to control agitation in these patients by prescribing neuroleptic medications. Neuroleptics sometimes reduce agitation, but only in a portion of demented patients.[3] In addition, the use of neuroleptics in elderly patients is frequently associated with major toxicity, including excessive sedation, falls, and tardive dyskinesia.

Despite the need to identify effective, nontoxic alternative treatments, controlled trials comparing neuroleptics to other treatments in agitated demented patients are few.[3] Some studies have compared neuroleptics to sedative medications;[14] however, sedatives often worsen demented patients' already impaired cognitive abilities and can increase the risk of falls in elderly patients.[15] There are no published clinical trials comparing the efficacy of a neuroleptic with that of an antidepressant in agitated patients with dementia. In this regard, the present pilot study is unique: it is the first randomized, double-blind, placebo-controlled investigation to directly compare an antipsychotic drug and an antidepressant for reduction of agitation in patients with AD.

Unfortunately, the small number of subjects in this pilot investigation severely limits the power of statistical analysis. A preliminary power analysis estimated that a study containing 60 subjects would be needed to provide 90% power to detect a clinically relevant difference

TABLE 1. Efficacy and toxicity data

Measure	Mean ± SD			*F* (df = 2,12)	*P*
	Haloperidol	Fluoxetine	Placebo		
CMAI				0.21	0.82
At baseline	37.4 ± 4.4	33.8 ± 3.0	34.4 ± 8.2		
At endpoint	35.0 ± 11.2	35.2 ± 10.3	33.0 ± 3.5		
BEHAVE-AD				1.16	0.35
At baseline	11.8 ± 4.9	7.0 ± 4.2	5.6 ± 3.4		
At endpoint	9.2 ± 7.1	8.8 ± 3.5	6.6 ± 3.5		
CSI				0.41	0.67
At baseline	165.4 ± 50.3	160.4 ± 121.8	116.2 ± 57.0		
At endpoint	179.4 ± 91.9	143.6 ± 79.3	134.8 ± 62.1		
Number of adverse symptoms	15.6 ± 2.4	15.4 ± 5.0	7.3 ± 7.6	3.82	0.05

Note: CMAI = Cohen-Mansfield Agitation Inventory; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; CSI = University of Iowa Caregiver Stress Inventory.

in efficacy between the groups with a type I error rate of 0.05. However, despite the small sample size, the present study was able to detect a significant difference in toxicity among the three treatments. This is an important finding, of which clinicians and clinical investigators should be aware. Much larger, multicenter studies will likely be needed to adequately determine whether significant differences in efficacy exist between neuroleptics and alternative treatments for agitation in patients with AD.

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