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Effect of a Serotonin Reuptake Inhibitor on Irritability, Apathy and Psychotic Symptoms in Patients with Alzheimer's Disease

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Abstract

Objective—To ascertain the impact of treatment with citalopram on irritability, apathy, delusions and hallucinations in non-depressed behaviorally disturbed Alzheimer's disease (AD) patients.

Method—This was a retrospective review of data from the 36-week CATIE trial in which AD patients were treated in a naturalistic manner with placebo, citalopram, risperidone, olanzapine or quetiapine, comparing scores on the Irritability, Apathy, Delusions and hallucinations subscales of the Neuropsychiatric Inventory.

Results—Of the 421 patients enrolled, 34 had been started on placebo and had been later randomized to citalopram treatment. There were data available for 34 subjects who had been on placebo for at least 14 days. In this group there was a 60% reduction in irritability and apathy scores, no effect on score for delusions, and a clinically insignificant drop in score for hallucinations.

Conclusion—The use of citalopram was associated with greatly reduced irritability without sedation in a group of behaviorally disturbed AD patients.

Keywords

Alzheimer disease; serotonin reuptake inhibitor; apathy; irritability; psychosis

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An extensive literature supports a role for serotonin deficit in the neurobiology of aggression and violence.[1] In 1976, Greenberg and Coleman noted that serotonin metabolite 5-hydroxyindole (5-HI) levels in blood were low in hyperactive institutionalized mentally retarded patients.[2] In these patients, increasing 5-HI levels in blood to within the normal range by administration of a variety of psychoactive agents was associated with reduced hyperactivity and calming. Patients who remained hyperactive continued to have low 5-HI levels. More recently, serotonin reuptake inhibitors (SRIs) were shown to reduce impulsive aggression in personality-disordered subjects.[3]

Alzheimer's disease (AD) is associated with an extensive serotonergic deficit[4] that might partly explain agitation and irritability in this disease; the dorsal raphe nucleus of brain stem, the site of serotonergic forebrain innervation, is markedly depopulated in AD patients[5] and Gottfries et al.[6] found that brain serotonin metabolites are reduced to 30–40% in AD patients.

At the clinical level, Nyth and Gottfries[7] reported significantly decreased irritability in 98 non-depressed persons with AD or vascular dementia after treatment with citalopram 20–30 mg/day for 4 weeks. In an open-label study of 16 dementia inpatients with behavioral problems treated with citalopram, disinhibition, agitation, hostility, suspicion were

significantly reduced after 17 days.[8] The drug was dosed at 10 mg/day for the first 72 hours, and then at 20 mg/day. A second study by the same investigators found that nondepressed persons with dementia admitted to a psychiatric inpatient unit for management of behavioral symptoms showed a significantly greater effect of citalopram 20 mg/day than placebo over a period of 17 days.[9] The outcome data were analyzed using last observation carried forward; about 50% of both groups had dropped out by that time, primarily due to perceived lack of efficacy. In this severely impaired group with mean Mini-mental State Exam[10] score < 10, citalopram-treated subjects had significantly greater improvement than placebo-treated subjects on the agitation and lability/tension scales of the Neuropsychiatric Inventory (NPI),[11] but not on the apathy scale. In a randomized 12-week study comparing citalopram with risperidone in 106 persons with dementia hospitalized for treatment of behavioral problems, both drugs were associated with an approximately 1/3 reduction in a measure of psychotic symptoms; citalopram was associated with a 13% decrease in a measure of agitation as compared with an 8% decrease for risperidone.[12]

A post hoc analysis of a randomized placebo-controlled study of sertraline in donepezil-treated AD patients used a 50% reduction from baseline in behavioral/psychological symptoms as the criterion level of response.[13] The study found that in AD patients experiencing agitation, irritability, anxiety, aggression and affective symptoms, sertraline augmentation resulted in response rate of 60% vs 40% on placebo, using the four-item NPI Behavioral and Psychological Symptom subscale, and 50% vs 32% using the three item BEHAVE-AD behavioral and mood subscale.[14]

If raising serotonin levels reduces irritability, it is likely that apathy might be increased, and a small body of literature suggests that dose-related apathy may occur in persons treated with SRIs for depression.[15] In addition, a retrospective study of 384 elderly depressed psychiatric inpatients treated with SSRI and non-SSRI drugs showed that a significantly greater proportion of subjects treated with SSRIs remained apathetic at discharge (83.7% of the SSRI group and 73.4% of the non-SSRI group; $p = 0.029$).[16]

We hypothesized that modest doses of a serotonin reuptake inhibiting drug (SRI) would decrease irritability in nondepressed AD subjects without significant increase of apathy.

METHOD

This was a retrospective study employing the database of the Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease (CATIE).[17] The CATIE study was a naturalistic study comparing the SRI citalopram with the antipsychotic drugs risperidone, olanzapine, quetiapine and with placebo for the treatment of psychosis, aggression, and agitation in persons with AD. Subjects were excluded from the study if they were currently or had been treated with 2 of the 3 atypical antipsychotic drugs. A 2-week washout of psychotropic drugs was preferred, but subjects were allowed to continue psychotropic drugs that were thought by the primary care physician to be helpful. The minimum duration of Phase 1 was 14 days. Phase 2 lasted a minimum of 2 weeks and a maximum of 12 weeks. Phase 1 consisted of randomization to treatment with placebo, risperidone, olanzapine, or quetiapine. Transition from Phase 1 to Phase 2 occurred at variable times at the discretion of the treating physician and was based often on lack of efficacy or undesirable side effects. In Phase 2, subjects were blindly randomized to citalopram, risperidone, olanzapine or quetiapine. Clinicians had the option of going on to Phase 3, in which they could prescribe open-label risperidone, olanzapine or quetiapine.

We examined data from subjects who were randomized initially to placebo (Phase 1) and subsequently randomized to citalopram 5–30 mg day (Phase 2), based on the judgment of

the treating clinician. We compared the Apathy and Irritability subscale scores of the NPI at the end of the placebo phase (Phase 1) with Apathy and Irritability scores at the end of the citalopram phase of the study (Phase 2).

The NPI is a administered to caregivers to retroactively assess behaviors observed in dementia patients, usually over a period of 1 month, but the observation period for this study was 1 week. The NPI covers 12 domains including: delusions, hallucinations, depression/dysphoria, anxiety, agitation/aggression, elation/euphoria, disinhibition, irritability/lability, apathy/indifference, aberrant motor activity, sleep, and appetite and eating disorders. Subscale scores are the product of frequency X severity scores. Scores for the Apathy and Irritability subscales range from 0–12, with higher scores indicating greater severity.

Subjects were screened for depression using a 21-item version of the Beck Depression Inventory (BDI).[18] Scale score range from 0–63, with higher scores indicating more severe depression. Scores <10 indicate no or minimal depression.

Statistical Analyses

Baseline median and range is presented for the BDI. To examine changes in the NPI Total Score and the subscales (apathy, irritability delusions and hallucinations), the last available scores in Phase 1 and Phase 2 for each patient were compared using the Wilcoxon Sign Ranks Test. A Spearman rank order correlation was used to compare the duration in Phase 2 with the maximum daily dose of citalopram. SPSS V16 was used for all analyses. Two-sided p-values < 0.05 were considered significant.

RESULTS

A total of 421 cases were available in the CATIE data base. Their demographics are presented elsewhere.[17] The study group for this investigation included the 44 subjects who received placebo as Phase 1 treatment and citalopram as Phase 2 treatment. The NPI scores analyzed represent the last testing performed before the end of each phase or at the last visit of the phase. The first visit for all patients was study day 1. The NPI was administered at weeks 0, 2, 4, 8, 12, 24, and 36; the BDI was administered at weeks 0, 12, 24, and 36. BDI scores at week 0 ranged from 10–20; median BDI was 10.

Forty-four patients received placebo in Phase 1 and citalopram in Phase 2. One subject did not have any data for all time points. One patient did not have data available for the end of Phase 1 (placebo) measurement; 8 did not have measurements for the end of Phase 2 (citalopram). For the remaining 34 subjects, the median Beck Depression Scale score at baseline was 10 (range 0–20). The median duration of Phase 1 was 36 days (range = 14 – 232 days); median duration of Phase 2 for the citalopram-treated group was 80 days (range = 14 – 306 days. Median daily dose of citalopram was 30 mg (range = 10–80 mg). The discontinuation rate for citalopram was 70%; slightly less than the discontinuation rates for placebo (85%), quetiapine (82%), risperidone (77%) and olanzapine (80%) in Phase 1. Of interest, there was a positive association between citalopram dosage and length of treatment with citalopram; $r(41) = 0.38$, $p = .015$.

The effects of placebo and citalopram on NPI total scores and scores on the Apathy, Irritability, Delusions, and Hallucinations subscales are presented in Table 1. Although the effect of the drug citalopram on apathy and irritability was not statistically significant, both apathy and irritability scores were reduced by 60%. This finding in behaviorally disturbed nondepressed AD patients differs from the finding in depressed elders of increased apathy associated with SRI antidepressants (as compared with non-SRIs).[16] We had expected no effect of citalopram on psychotic symptoms, and although there was a significant reduction

in the Hallucinations subscale of the NPI, these symptoms were of low frequency and intensity, as indicated by a median score of 1 point. There was no effect on delusions.

Discussion

There are a number of confounds in examining the effects of psychotropic medications in the management of behavioral symptoms in dementia, including the placebo response. For example, one-third of persons with behavioral problems associated with AD improved on placebo in a 16-week controlled trial.[19] This outcome could also have been attributable to more frequent visits and related support for patient and caregiver. Another, and more likely explanation, is a regression to the mean.[20] Dementia-related behaviors tend to be intermittent, differing in this respect from syndromes such as major depression. Caregivers seek help with dementia-related behaviors when they peak; thus, improvements attributed to medication may equally well be due to the passage of time or greater tolerance of the caregiver for the behavior(s). In this study, the placebo effect was an unlikely cause of improvement in that this was the second phase of the study rather than the initial phase.

CONCLUSIONS

Although it is not clear that the improvement was due to its serotonergic action, use of an SRI was followed by a large decrease in irritability of nondepressed AD patients with a concomitant decrease in apathy. There was no effect on delusions. Although statistically significant, the effect on hallucinations did not appear clinically meaningful in view of their low frequency and intensity. Based on these findings, and considering the potential toxicity, side effects and sedation produced by all antipsychotic agents,[21] the considerable expense of second-generation antipsychotics, the sedation and ataxia associated with minor tranquilizers and the relative lack of toxicity and side effects and the low cost of many SRIs, an SRI might be reasonable first-line treatment for irritability in AD patients. The positive association between citalopram dose and length of treatment with citalopram suggests that there may be a tendency to underdose with this drug or class of drugs and that titration to higher than ordinary antidepressant doses may be indicated. In any eventuality, a larger trial seems indicated.

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Table 1

Neuropsychiatric Inventory (NPI) Total Score, Apathy, and Irritability Subscale Scores for Patients Treated with Citalopram (N=34)

					Percentiles		
Scale	**Time**	**Median**	**Minimum**	**Maximum**	**25**	**75**	**Wilcoxon Test p-value**
Total NPI	End Phase 1	33.00	8	78	29.25	49.0	.089
	End Phase 2	25.00	1	78	16.00	46.5	
Apathy	End Phase 1	5.00	0	12	1.00	8.0	.099
	End Phase 2	2.00	0	12	.00	6.0	
Irritability	End Phase 1	6.00	0	12	3.00	8.0	.739
	End Phase 2	3.50	0	12	.00	8.0	
Delusions	End Phase 1	3.50	0	12	0.0	8.0	.780
	End Phase 2	3.50	0	12	0.0	8.0	
Hallucinations	End Phase 1	1.00	0	8	0.0	6.0	.022
	End Phase 2	0.50	0	12	0.0	6.0	

Wilcoxon Signed Ranks Test

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