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Olanzapine in the treatment of anxiety symptoms due to Alzheimer's disease: a post hoc analysis

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SUMMARY

Background Alzheimer's disease (AD) is associated with both cognitive and behavioral symptoms. Agitation, hallucinations, delusions, aggression, irritability, and anxiety are observed in up to 90% of patients with dementia. Although new information has emerged in recent years on the treatment of psychosis and agitation in dementia, very little information is available about the treatment of anxiety symptoms in this population.
Objectives To assess the efficacy and tolerability of olanzapine in the treatment of significant anxiety symptoms in patients with AD.
Methods A *post hoc* analysis of a previously published study was performed. Those post hoc analysis evaluated the response to treatment with olanzapine of a subgroup of AD patients presenting with significant symptoms of anxiety. Patients were considered to have significant symptoms of anxiety if their baseline in the Nursing home version of the Neuropsychiatric Instrument NPI/NH anxiety scores were ≥ 2. The analysis included 120 patients.
Results Patients receiving olanzapine 5 mg/d were statistically significantly improved on the NPI/NH *Anxiety* item compared to those receiving placebo (olanzapine, 5 mg/d: -3.72; placebo: -1.67; $p = 0.034$). In the group of patients with clinically significant anxiety, somnolence was the only treatment-emergent event that was statistically different in any olanzapine treatment group compared with placebo (olanzapine 5 mg/d: 9 patients [25%], $p = 0.034$; 10 mg/d: 7 [23%], $p = 0.054$; 15 mg/d: 7 [26%], $p = 0.050$; placebo: 1 [3.7%]). When controlling for treatment-emergent somnolence, the improvement in anxiety in the olanzapine 5 mg/d group remained statistically significant ($p = 0.049$).
Conclusions These findings suggest that olanzapine could be a safe and effective treatment for anxiety in Alzheimer's disease. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — Behavioral and Psychological Symptoms of Dementia (BPSD); Alzheimer's disease; anxiety; pharmacological treatment; atypical antipsychotics

INTRODUCTION

Alzheimer's disease (AD) is associated with both cognitive and behavioral symptoms. Agitation, hallucinations, delusions, aggression, irritability, and anxiety are observed in up to 90% of patients with dementia (Tariot and Blazina, 1994). Their presence in AD patients has devastating consequences, including a negative impact on patients' levels of stress (Zarit *et al*., 1986), caregiver burden (Nagaratnam *et al*., 1998), and the need for nursing home placement (Zarit *et al*., 1986; Steele *et al*., 1990). Anxiety in patients with AD has received little attention (Mintzer *et al*., 2000). Frequently, anxiety in AD is viewed by clinicians as synonymous with other behaviors, notably agitation and aggression (Mintzer and Brawman-Mintzer, 1996), or as a component of a broader syndrome, such as psychosis or depression (Mega *et al*., 1996). However, anxiety as a specifically defined syndrome is identified in up to 48% of patients with AD

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(Reisburg *et al*., 1987; Burns *et al*., 1990; Mega *et al*., 1996). In a study of 523 community-dwelling AD patients, Teri *et al*. (1999) found anxiety to be as frequent as 44%.

As a result of this high prevalence and negative impact, there is a need for effective treatment of behavioral disturbances such as anxiety in AD. A variety of medications, including benzodiazepines and selective serotonin reuptake inhibitor (SSRI) antidepressants, is used in the management of anxiety and other behavioral symptoms due to dementia (Nyth and Gottfries, 1990; Algozzine *et al*., 1999). Regardless of their efficacy, benzodiazepines are not recommended as first-line treatment in this patient population for behavioral symptoms, including anxiety and sleep disturbance (Stern *et al*., 1991; Patel and Tariot, 1995; Borson and Raskind, 1997), because of their negative impact on cognition. SSRI antidepressants (Nyth and Gottfries, 1990) and compounds with serotonergic receptor affinity, such as buspirone (Herrmann and Eryavec, 1993; Sakauye *et al*., 1993) and trazodone (Houlihan *et al*., 1994; Lebert *et al*., 1994), have been found to affect a broad spectrum in the behaviorally disturbed AD patient; however, their efficacy and safety still need to be proven. Antipsychotics have been the most widely examined for treatment of behavioral disturbances. The use of conventional agents such as haloperidol has been reported to be efficacious in the treatment of psychosis (hallucinations and delusions) (Devanand *et al*., 1989, 1998). These medications, however, are associated with unwanted effects including hypotension and extrapyramidal symptoms (Small *et al*., 1997; Devanand *et al*., 1998). The atypical antipsychotics, including risperidone, quetiapine, and olanzapine, have been shown to be efficacious in the treatment of psychosis and agitation/aggression with a more favorable safety profile for the elderly (De Deyn *et al*., 1999; Katz *et al*., 1999; McManus *et al*., 1999; Street *et al*., 2000).

Both conventional and atypical antipsychotics have been reported to be effective only in reducing agitation/aggression, hallucinations, and delusions in patients with dementia. The efficacy of these agents in the treatment of anxiety remains unknown. This is a *post hoc* analysis assessing the efficacy and tolerability of an atypical antipsychotic, olanzapine, in the treatment of anxiety in patients with AD. Data were obtained from a previously reported multicenter, double-blind clinical trial (Street *et al*., 2000) evaluating the efficacy of olanzapine versus placebo in the treatment of hallucinations, delusions, and agitation/aggression due to AD.

PATIENT SELECTION

Patients eligible for the study at large (Street *et al*., 2000) were at least 40 years of age, nursing home residents, and met the criteria for possible or probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (McKhann *et al*., 1984). Patients were required to have a score of $\geqslant 3$ (suggesting at least moderate frequency and/or severity) on any of the Neuropsychiatric Inventory/Nursing Home version (NPI/NH) (Wood *et al*., 2000) *Agitation/Aggression*, *Delusions*, or *Hallucinations* items and a score of < 25 on the Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975). Patients were excluded if they were bedridden, had a history of an Axis I disorder within 12 months before study entry, or any other diagnosis of a serious neurological condition other than AD that could contribute to psychosis or dementia. Concomitant medications with primarily central nervous system activity, such as cholinesterase inhibitors, anticonvulsants, mood stabilizers, other antipsychotics, tricyclic and monoamine oxidase inhibitor antidepressants, and anticholinergics were not allowed. Patients were permitted to use SSRI antidepressants but were not allowed to alter the medication after screening. This provision was made to allow enrollment of patients with chronic depression without confounding the assessment of treatment-emergent signs and symptoms with potential side effects that could arise from weaning patients off their regular medications. Institutional review board approval was obtained, and patients or their legal representatives all gave written informed consent after a complete description of the study was presented.

For the purpose of this study, a subset of patients was evaluated who presented with clinically significant anxiety symptoms, defined as a score of $\geqslant 2$ on the NPI/NH *Anxiety* item (at least moderate severity [stressful for the resident and difficult to change by the caregiver] or often in frequency (about once per week)).

DESIGN

This double-blind, placebo-controlled 6-week study (Street *et al*., 2000) was conducted at 28 sites in the United States from December 1996 through June 1998. After a washout and placebo lead-in period of 3–14 days, patients were randomly assigned at each site using a permuted block design provided by the sponsor (Lilly Research Laboratories) to one of four

fixed-dose treatment groups (placebo; olanzapine 5, 10, or 15 mg/d) administered once daily. All patients assigned to olanzapine therapy began at 5 mg/d, with subsequent increases of 5 mg every seven days for those patients assigned to the 10 and 15 mg/d groups.

Patients were evaluated at baseline and weekly for up to 6 weeks. Efficacy assessments consisted of the NPI/NH, including the individual items of *Delusions*, *Hallucinations*, *Agitation/Aggression*, and *Anxiety*, and the Brief Psychiatric Rating Scale (BPRS) (Guy, 1976). The NPI (Cummings *et al*., 1994) and its Nursing Home version (Wood *et al*., 2000) are caregiver-rated scales that assess psychopathology in dementia and consist of ten behavioral and two neurovegetative items. Each item is operationally defined for the specifically focused behavior. Anxiety is defined as nervousness, worry or fear for no reason, tension, and/or fear of being separated from a trusted caregiver. If a behavior is present, the scale assesses severity (1 = mild to 3 = marked) multiplied by frequency (1 = occasionally to 4 = very frequently), for a possible item score ranging from 1–12. The impact of each reported behavior upon the professional caregiver is assessed by the Occupational Disruptiveness scale (0 = none to 5 = very severely/extremely).

Tolerability and safety were measured with the Simpson—Angus Scale (Simpson and Angus, 1970), Abnormal Involuntary Movement Scale (Guy, 1976), and Barnes Akathisia Scale (Barnes, 1989) for extrapyramidal symptoms (EPS), and cognitive function was measured by the MMSE, an 11-item rating scale with a score range of 0–30. Additional assessments included reports of treatment-emergent adverse events, vital signs, weight, standard laboratory analyses, and electrocardiographic (ECG) parameters. Benzodiazepines were utilized as rescue medication, up to 4 mg/d lorazepam-equivalents and a total of 21 days during the treatment period.

STATISTICS

Mean change from baseline to endpoint (last-observation-carried-forward [LOCF], unless otherwise noted) was analyzed using analysis of variance (ANOVA). The Fisher's Exact test was used to analyze categorical data to determine statistical significance.

RESULTS

Patient characteristics

A detailed description of the characteristics of the population of the study at large can be found elsewhere (Street *et al*., 2000). Briefly, 288 participants entered the placebo washout period, and 206 were randomly assigned to double-blind treatment with olanzapine 5 mg/d ($n = 56$), 10 mg/d ($n = 50$), 15 mg/d ($n = 53$), or placebo ($n = 47$). The subjects ranged in age from 61 to 97 years (mean: 82.8 y), and 126 (61%) were female. The overall mean MMSE baseline score was 6.7 ± 6.4, with approximately 71% of subjects severely cognitively impaired (MMSE score $\leqslant 10$). The average time from nursing home admission to study entry was 19 months. At baseline, 95.0% of patients randomized into the study exhibited agitation/aggression while 57.9% had both agitation/aggression and at least one psychotic symptom. The mean baseline score for anxiety in the overall study was 4.26 (range: 3.63 to 4.45).

As discussed above, a subset of patients was evaluated who presented with clinically significant anxiety symptoms, defined as an NPI/NH *Anxiety* item score $\geqslant 2$ (at least moderate severity (stressful for the resident and difficult to change by the caregiver) or often in frequency (about once per week)). There were no statistically significant differences across treatment groups in baseline characteristics of this subset (see Table 1).

This patient subgroup of 120 subjects, 58.3% of the entire study population, was predominantly female (71.67%), evenly divided between those up to 85 years of age and those 85 or older (52.50% and 47.50%, respectively), and had a mean baseline MMSE score of 7.43 ± 6.24. The majority (70.83%) was severely cognitively impaired. The mean baseline anxiety score for this patient subset was 7.23 ± 3.13, with women having higher baseline scores than men (7.63 *vs* 6.24, respectively). Among patients with clinically significant anxiety, 65.00% also demonstrated item scores of $\geqslant 3$ at baseline on NPI/NH *Delusions*, 29.17% on *Hallucinations*, 95.00% on *Agitation/Aggression*, and 44.17% on *Depression*. The mean baseline score for the NPI/NH *Depression* item in all treatment groups in the patient subset was low, as well as for the overall study, suggesting that depression was not identified as a potentially influential comorbid clinical condition in either patient population.

EFFICACY

Within the overall study of 206 subjects, low dose-olanzapine (5 and 10 mg/d) was more effective than placebo at reducing psychosis (delusions and hallucinations) (mean change: placebo: -1.62; olanzapine 5 mg/d: -3.60, $p = 0.001$; 10 mg/d: -2.20, $p =$

Table 1. Baseline patient characteristics anxiety subgroup

Characteristic	Placebo	Olz 5 mg/d	Olz 10 mg/d	Olz 15 mg/d
n	27	36	30	27
Ethnic Origin, *n* (%)				
Caucasian	26 (96.3%)	33 (91.7%)	30 (100.0%)	24 (88.9%)
African-American	1 (3.7%)	1 (2.8%)	0 (0.0%)	3 (11.1%)
Hispanic/Other	0 (0.0%)	2 (5.6%)	0 (0.0%)	0 (0.0%)
Age, years				
Mean (SD)	81.67 (6.44)	82.73 (6.20)	84.78 (5.58)	83.74 (6.62)
Range	(69.80, 94.50)	(68.20, 91.50)	(67.80, 97.70)	(69.20, 94.00)
Sex, n (%)				
Male	8 (29.6%)	11 (30.6%)	8 (26.7%)	7 (25.9%)
Female	19 (70.4%)	25 (69.4%)	22 (73.3%)	20 (74.1%)
Severe Cognitive Impairment, *n* (%)	22 (18.3%)	24 (20.0%)	21 (17.5%)	18 (15.0%)
MMSE Baseline Scores Mean (SD)	6.07 (5.53)	8.36 (6.64)	7.47 (6.18)	7.48 (6.51)
NPI/NH Anxiety Baseline Scores Mean (SD)	6.74 (3.13)	7.42 (3.13)	7.73 (3.06)	6.93 (3.28)

0.037). Olanzapine 15 mg/d was numerically superior to placebo in reducing psychosis, but this difference was not significant (mean change: olanzapine 15 mg/d, -1.86; placebo, -1.62; $p = 0.202$). Patients treated with olanzapine 5 mg/d had a statistically significant reduction on the *Anxiety* item as compared to placebo (-1.98 and -0.62, respectively; $p = 0.008$). This improvement was likewise reflected in the occupational disruptiveness score, with a statistically significant difference between olanzapine 5 mg/d and placebo (-0.33 and -0.71, respectively; $p = 0.035$). There were no significant changes in MMSE scores from baseline for any olanzapine group compared with placebo.

In this study subset, patients assigned to olanzapine 5 mg/d were statistically significantly improved on the NPI/NH *Anxiety* item compared with patients assigned to placebo (olanzapine 5 mg/d: -3.72; placebo: -1.67; $p = 0.034$; see Figure 1). This

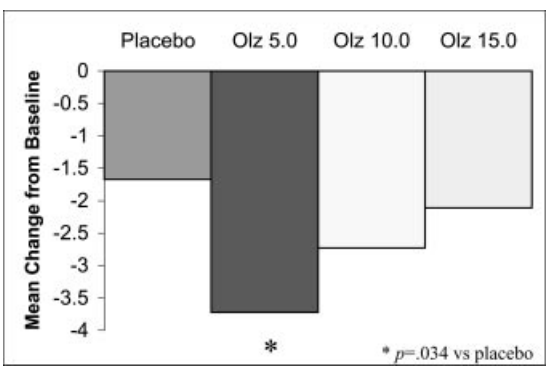

Figure 1. Mean change from baseline to LOCF endpoint for NPI/NH *Anxiety* score

improvement was likewise reflected in the Occupational Disruptiveness score, although not statistically significant. Changes from baseline in MMSE scores were small, -0.85 to 1.06, and these were not statistically significantly different across treatment groups.

Because patients entering the study presented with clinically significant levels of hallucinations, it could be argued that changes in anxiety were secondary to the improvement in these baseline behaviors. When controlling for the improvement in hallucinations from baseline to endpoint, the improvement in anxiety in the olanzapine 5 mg/d treatment group remained statistically significant ($p = 0.024$).

SAFETY AND TOLERABILITY

In the larger study group, there were no statistically significant differences among the olanzapine-treated groups as compared to placebo with regard to objectively assessed EPS using the Simpson–Angus Scale, AIMS, or the Barnes Akathisia Scale. Somnolence and abnormal gait (stooped posture, unsteady gait, leaning, ambulation dysfunction) were the only significant treatment-emergent adverse events in the olanzapine groups compared to placebo. Additionally, there were no clinically significant differences for mean changes in vital signs (including orthostasis or weight gain or loss), laboratory analyses, or ECG parameters (including corrected QT intervals (QT_c)) for participants treated with olanzapine as compared with placebo.

In the group of patients with clinically significant anxiety, somnolence was the only treatment-emergent event that was statistically different in any olanzapine treatment group compared with placebo (placebo: 1 (3.7%); olanzapine 5 mg/d: 9 patients (25%),

$p = 0.034$; 10 mg/d: 7 (23%), $p = 0.054$; 15 mg/d: 7 (26%), $p = 0.050$). When controlling for treatment-emergent somnolence, the improvement in anxiety in the olanzapine 5 mg/d group remained statistically significant ($p = 0.049$).

Incidence of treatment-emergent abnormal gait was not statistically different from placebo at any olanzapine dose. Likewise, none of the individual peripheral or central potential anticholinergic adverse events occurred more frequently in any olanzapine treatment group compared with placebo. (Central activity event terms included agitation, confusion, delirium, delusions, dyskinesia, fever, hallucinations, thinking abnormal, and twitching. Peripheral terms included amblyopia, constipation, dry mouth, dry skin, fecal impaction, fever, intestinal obstruction, tachycardia, urinary retention, and vasodilation.) However, when peripheral anticholinergic treatment-emergent adverse event COSTART terms were pooled, there was a significant difference in the incidence of this class of events in the olanzapine 15 mg/d treatment group compared with placebo (26.4% *vs* 6.38%, $p = 0.008$). Pooling of central anticholinergic treatment-emergent adverse event COSTART terms did not lead to any statistical difference between treatment groups.

To closely evaluate safety in the most frail group, an additional subgroup analysis of patients with clinically significant anxiety (< 85 and $\geqslant 85$ years of age) was conducted. In patients < 85 years of age with anxiety, ecchymosis was identified more often in the placebo group (Five patients, 26%) compared with any dose of olanzapine (5 mg/d: 0 patients, $p = 0.018$; 10 mg/d: 0, $p = 0.134$; 15 mg/d: 1 (7.7%), $p = 0.361$). Somnolence was identified more often in the olanzapine patients than in placebo patients (5 mg/d: six patients (28.57%), $p = 0.021$; 10 mg/d: two patients (20.00%), $p = 0.111$; 15 mg/d: three patients (23.08%), $p = 0.058$). In the older age group ($\geqslant 85$ years), no adverse events occurred with statistical significance between any olanzapine treatment group and placebo.

Objective EPS assessments showed no statistically significant differences between olanzapine and placebo-treated patients with clinically significant anxiety. There were no clinically meaningful differences between olanzapine treatment groups and placebo in changes in vital signs (including weight and orthostasis), laboratory analytes, and ECG intervals (including QT_c) among patients with clinically significant anxiety. Approximately 76% of patients (91/120) in the anxiety subgroup completed the study, compared with 73.79% (152/206) in the overall study. Of the 29 patients discontinuing prior to completion, 11 patients left the study due to an adverse event, five due to lack of efficacy, four for patient decision, four because of the sponsor's decision, two related to physician's decision, and three because study criteria because of noncompllance.

Since benzodiazepines were used as rescue medication, it could be argued that the differences observed could be attributed to a differential use of benzodiazepines among groups, so data were analyzed controlling for the use of benzodiazepines as rescue medication. The improvement in anxiety for the olanzapine 5 mg/d treatment group relative to placebo remained statistically significant with the adjusted model (-3.72 *vs* -1.67, $p = 0.044$).

DISCUSSION

The present study is the first addressing the question of the efficacy of atypical antipsychotics in the treatment of anxiety symptoms due to AD. Our data indicate low-dose (5 mg/d) olanzapine is superior to placebo in the treatment of anxiety symptoms in patients with AD. The superiority of the low-dose group over the two higher-dose groups is consistent with the response seen in the larger study of 206 patients in the treatment of hallucinations, delusions, agitation/aggression, and anxiety due to AD (Street *et al*., 2000). It is also consistent with other double-blind trials showing a low-dose response with similar compounds, such as risperidone (1–2 mg/d) for the treatment of behavioral disturbances in patients with AD, such as psychosis and aggression (De Deyn *et al*., 1999; Katz *et al*., 1999). The inverse dose–response curve in this patient population is detailed elsewhere (Street *et al*., 2000) and suggests a number of patient and compound characteristics of particular relevance to the study population. The demographic characteristics of the subgroup were not different from the overall study population. However, the mean baseline anxiety score was greater in the subgroup compared with the mean baseline anxiety score for the overall study, identifying a patient population with a clinically significant behavior that warrants further study.

Psychosis due to AD has been identified by the United States Food and Drug Administration Psychopharmacological Drugs Advisory Committee Meeting on the Various Psychiatric and Behavioral Disturbances Associated with Dementia (March 9, 2000) as a distinct syndrome and warranting an indication for pharmacological therapy. Consideration of other areas of behavioral disturbances in patients with

dementia, including anxiety, may also warrant such evaluation.

Although these data represent a *post hoc* analysis, this report serves as a pilot for the consideration of additional studies that prospectively will target treatment strategies in AD patients suffering from clinically significant anxiety. We believe this study to be hypothesis generating and require follow up with studies defining *a priori* appropriate measurement tools and delineation of the patient population. The findings from this patient subset need to be reaffirmed in both nursing-home and community dwelling populations, along with assessments of caregiver impact.

It is relevant to note that the statistically significant improvement of anxiety in this subset of patients treated with olanzapine 5 mg/d was not secondary to an improvement in hallucinations, treatment-emergent somnolence, or benzodiazepine use. These data suggest that low dose olanzapine (5 mg/d) may offer a safe, well-tolerated treatment option for AD patients with anxiety.

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