Olanzapine Treatment of Psychotic and Behavioral Symptoms in Patients With Alzheimer Disease in Nursing Care Facilities

A Double-blind, Randomized, Placebo-Controlled Trial

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Background: Patients with Alzheimer disease (AD) commonly exhibit psychosis and behavioral disturbances that impair patient functioning, create caregiver distress, and lead to institutionalization. This study was conducted to assess the efficacy and safety of olanzapine in treating psychosis and/or agitation/aggression in patients with AD.

Methods: A multicenter, double-blind, placebocontrolled, 6-week study was conducted in 206 elderly US nursing home residents with AD who exhibited psychotic and/or behavioral symptoms. Patients were randomly assigned to placebo or a fixed dose of 5, 10, or 15 mg/d of olanzapine. The primary efficacy measure was the sum of the Agitation/Aggression, Hallucinations, and Delusions items (Core Total) of the Neuropsychiatric Inventory–Nursing Home version.

Results: Low-dose olanzapine (5 and 10 mg/d) produced significant improvement compared with placebo on the Core Total (-7.6 vs -3.7 [P<.001] and -6.1 vs -3.7 [P=.006], respectively). Core Total improvement with olanzapine, 15 mg/d, was not significantly greater than placebo. The Occupational Disruptiveness score, reflecting the impact of patients' psychosis and behavioral disturbances on the caregiver, was significantly reduced in the 5-mg/d olanzapine group compared with placebo (-2.7 vs -1.5; P=.008). Somnolence was significantly more common among patients receiving olanzapine (25.0%-35.8%), and gait disturbance occurred in those receiving 5 or 15 mg/d (19.6% and 17.0%, respectively). No significant cognitive impairment, increase in extrapyramidal symptoms, or central anticholinergic effects were found at any olanzapine dose relative to placebo.

Conclusion: Low-dose olanzapine (5 and 10 mg/d) was significantly superior to placebo and well tolerated in treating agitation/aggression and psychosis in this population of patients with AD.

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ATIENTS WITH Alzheimer disease (AD) manifest not only progressive memory impairment, cognitive deficits, and functional alterations but also a variety of neuropsychiatric disturbances

(agitation, aggression, hallucinations, delusions). These symptoms ultimately affect up to 75% of individuals with dementia1-6 and, once present, tend to be sustained or recurrent. A longitudinal assessment of 181 outpatients with AD and aggression or psychosis showed they were likely to exhibit recurrence of those symptoms during the following year (93% and 95%, respectively).7 Jeste and Finkel8 suggest the presumed disappearance of psychotic symptoms in patients with advanced stages of dementia could reflect an apparent, rather than real, remission because of patients' inability to articulate their delusions and hallucinations. Neuropsychiatric disturbances can affect caregivers and the overall management of the patient, including institutionalization and treatment choices. Despite the prevalence and impact of these disturbances, few studies have investigated the effect of patients' behaviors on staff at nursing care facilities. Neuropsychiatric symptoms may affect quality of patient care, increase staff supervision, and produce staff distress.^{9,10}

In nursing facilities, almost 46% of residents receive psychoactive medications, including antipsychotics (17%), anxiolytics (15%), antidepressants (24%), and hypnotic agents (5%).¹¹ Although antipsychotics have been the treatment of choice for psychobehavioral disturbances, a metaanalytic review of 33 studies comparing conventional antipsychotics with placebo in older, severely demented patients with agitation found these agents were modestly superior to placebo.¹² A placebo-controlled dose comparison of haloperidol for psychosis and disruptive behaviors in 71 outpatients with AD revealed a positive treatment effect for the 2- to 3-mg/d dose

PATIENTS AND METHODS

STUDY GROUP

Patients were elderly nursing care facility residents, initially screened on the basis of chart reviews, staff interviews, and recommendations by the investigators and patients' family members, who met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for possible or probable AD.16 For study inclusion, patients must have scored 3 or higher on any of the Agitation/ Aggression, Hallucinations, or Delusions items of the Neuropsychiatric Inventory-Nursing Home version (NPI/ NH)¹⁷ at screening and following a single-blind, placebo lead-in. A score of 3 or higher correlates with a clinically significant level of psychotic or behavioral symptoms, corresponding with moderate severity or frequency. Exclusion criteria included a history of a DSM-IV18 Axis I disorder (eg, schizophrenia, bipolar disorder, severe or recurrent depression), any neurological condition other than AD that could contribute to psychosis or dementia, a Mini-Mental State Examination (MMSE)¹⁹ score of greater than 24, and bedridden status. Before participation, all patients and/or their designated representative signed an informed consent document approved by the study site's institutional review board.

STUDY DESIGN

This was a 6-week, double-blind, placebo-controlled study of 206 randomized patients conducted at 28 sites, with a mean \pm SD enrollment of 7.4 \pm 7.2 patients per site (range, 0-29). Participants entered a 3- to 14-day, single-blind washout, placebo lead-in period. Patients who demonstrated a placebo response during the lead-in (\geq 50% decrease in Core Total; see "Assessments" section) were screened from the study. Patients meeting enrollment criteria were randomly allocated to 1 of 4 fixed-dose treatment groups (olanzapine, 5, 10, or 15 mg/d, or placebo) by the assignment of a unique kit number using a permuted block design at

group. However, 20% developed moderate-to-severe extrapyramidal symptoms (EPS). Although doses lower than 1 mg/d produced fewer EPS, they were less effective.¹³

Newer antipsychotic agents have significantly fewer adverse effects than conventional neuroleptics such as haloperidol,¹⁴ and investigation of these newer compounds in treating behavioral symptoms of AD is warranted. Olanzapine has been shown to be effective and well tolerated in a geriatric patient population with schizophrenia.¹⁵ To test the hypothesis that olanzapine provides safe and effective treatment for behavioral and psychotic disturbances in patients with AD, a double-blind study comparing 3 fixed doses of olanzapine to placebo was conducted among symptomatic nursing facility residents.

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

A total of 288 patients signed informed consent, with 206 randomized and 200 providing at least 1 postbaseline data

each investigational site (block size of 4). Study medication was in identical tablets and dosed once daily. Patients randomized to the 10- or 15-mg/d groups began treatment with 5 mg/d and were titrated to the target dose by 5-mg/d increments every 7 days. Patients unable to tolerate the assigned treatment were discontinued from the study.

The use of concomitant medications with primarily central nervous system activity was exclusionary, including anticholinergic agents, cholinesterase inhibitors, anticonvulsants, mood stabilizers, other antipsychotics, and tricyclic antidepressants. Benzodiazepines were allowed as rescue medication but could not exceed 4 mg/d of lorazepam equivalents for a total of 21 days during active treatment.

ASSESSMENTS

All patient assessments were conducted at the nursing facility by health care professionals, including neurologists, psychiatrists, geriatricians, psychometrists, nurses, and other medical specialists trained before study initiation. The NPI²⁰ evaluates psychopathology in patients with AD and other dementias. The reliability and validity of the NPI/NH have been established using nursing home patients.¹⁷ Responses are obtained by a trained interviewer from professional caregivers involved in the ongoing care of the patient in the previous week. The NPI/NH consists of 10 behavioral and 2 neurovegetative items, with the score of each item, if present, representing the product of symptom frequency (1=occasionally to 4=very frequently) times severity (1=mild to 3=severe). For each item, an Occupational Disruptiveness score is obtained and encompasses the work, effort, time, or distress a particular behavior causes the staff caregiver (0=no disruption to 5=very severe or extreme).^{17,21,22}

The primary efficacy measure consisted of the mean change from baseline to end point in the sum of the NPI/NH item scores for the core symptoms: Agitation/Aggression, Hallucinations, and Delusions (Core Total; range, 0-36). The Core Total was used to classify patients as responders

Continued on next page

point (Figure 1). Two patients were screened out as placebo responders. The demographic characteristics of the 82 nonrandomized patients were similar to the 206 randomized patients. Fifty-two (43 randomized, 9 nonrandomized) discontinued use of antipsychotics, primarily because of lack of efficacy or adverse reactions, within 30 days before randomization. Patient demographics and illness characteristics were similar across treatment groups (Table 1). Patients had a mean age of 82.8 years; most were white (92.7%) and female (61.2%). Average time since nursing facility admission to study entry was 1.6±1.1 years; onset of AD symptoms to study entry was 4.8±4.1 years; and time from diagnosis to study entry was 2.2±1.6 years. The overall mean baseline MMSE score was 6.7 ± 6.4. Baseline MMSE scores identified 70.9% of the study population as severely cognitively impaired (score, ≤ 10), 25.7% as moderately impaired (score, 11-20), and 3.4% as mildly impaired (score, 21-24). At study entry, 95.0% of patients had symptoms of agitation/aggression, 56.4% had delusions, 22.8% had hallucinations, and 57.9% had agitation/aggression and at least 1 psychotic symptom.

(≥50% reduction from baseline) and nonresponders. Secondary efficacy measures included mean changes from baseline to end point on the NPI/NH Total, Hallucinations and Delusions total (Psychosis Total), individual items, Occupational Disruptiveness score derived from the Agitation/ Aggression, Hallucinations, and Delusions items (Core Disruptiveness), Brief Psychiatric Rating Scale (BPRS)²³ total and subscale, and MMSE.¹⁹

Three scales objectively assessed EPS: Simpson-Angus Scale,²⁴ Barnes Akathisia Scale,²⁵ and Abnormal Involuntary Movement Scale.²⁶ At screening, medical history taking, psychiatric assessment, physical examination, and electrocardiography (ECG) were performed. The physical examination and ECG were repeated at end point and on discontinuation following randomization. Assessment of vital signs (blood pressure, pulse, weight, temperature) and clinical laboratory testing (chemistry, electrolytes, hematology) were performed. Efficacy and safety were assessed weekly and on discontinuation.

STATISTICAL ANALYSES

A sample size of approximately 200 patients was required to achieve 80% power to detect a difference among treatment groups of at least 2.0 points in the last observation carried forward mean change on the Core Total at a 2-tailed level of α =.05. Primary analyses were performed on an intent-to-treat basis as defined by Gillings and Koch²⁷ (patients with a baseline and at least 1 postbaseline measurement). Investigators with fewer than 1 patient per group for any treatment were pooled for statistical analysis.

All statistical tests were defined a priori in the protocol except the post hoc assessments of the Simpson-Angus Gait item, pooled potential anticholinergic effects, and correlations among adverse events. All tests were 2-sided, and pairwise comparisons among each of the 3 olanzapine groups and the placebo group were conducted. However, pairwise comparisons among the olanzapine groups were not systematically performed. For the primary analysis, a Bonferroni adjustment to the type I error rate for the 3 pairwise comparisons requires significance to be defined at α = .017. For all other analyses, reported *P* values were unadjusted for multiple comparisons since they were exploratory, but conclusions are based on consideration of this multiplicity.

Mean change in the scores was analyzed using a lastobservation-carried-forward analysis of variance (ANOVA) model that included terms for treatment, investigator (site), and treatment-by-investigator interaction. Temporal change on the Core Total used a repeated-measures analysis. This linear model included terms (considered fixed effects) for the baseline score, treatment, investigator, treatment-by-investigator interaction, visit, and treatmentby-visit interaction, and least squares means were reported. Estimates of effects were assessed by the method of restricted maximum likelihood, and an unstructured covariance matrix for the within-patient error was specified. Categorical analysis of the percentage of responders $(\geq 50\%$ reduction, baseline to end point) was performed using the Fisher exact test. Secondary efficacy variables were analyzed using the ANOVA model described for the primary efficacy measure.

Analyses of continuous measures of safety (laboratory analytes; ECG intervals: PR, QRS, QT, and corrected QT [QTc]; vital signs; EPS scales) were performed using last observation carried forward ANOVA models (mean changes from baseline to end point), including effects for treatment, investigator, and treatment ×investigator interaction. Categorical analyses of laboratory values, vital signs, ECG parameters, and treatmentemergent adverse events were conducted using the Fisher exact test. The proportions of patients with a Barnes Akathisia Scale score of 2 or higher at baseline and less than 2 at any postbaseline visit were compared among treatment groups by the Fisher exact test. A similar categorical analysis was conducted on the proportion of patients whose Simpson-Angus Scale score was 3 or less at baseline and increased to greater than 3 at any postbaseline visit.

Data are presented as mean±SD.

The proportion of patients completing the 6-week, double-blind therapy was 76.6% in the placebo group and 80.4%, 72.0%, and 66.0% in the 5-, 10-, and 15-mg/d olanzapine groups, respectively. Use of lorazepam equivalents (mean [SD] daily dose, 0.4 ± 0.5 mg/d) among patients taking benzodiazepines (46.1%, 95/206) was not significantly different in the 4 treatment groups. No significant differences were seen between completers and noncompleters regarding characteristics or baseline scores except NPI/NH Apathy and BPRS Negative Symptoms subscale, which were significantly worse among noncompleters (2.38 ± 3.34 vs 3.88 ± 4.94 [t_1 =2.39, P=.02] and 4.09±3.53 vs 6.50±5.41 [t_1 =3.35, P<.001], respectively).

EFFICACY RESULTS

On the Core Total, the 5- and 10-mg/d olanzapine groups experienced significantly greater improvement than the placebo group (**Table 2**). Patients receiving 5 mg/d improved by 7.6 \pm 7.7 points (placebo improvement, 3.7 \pm 10.3; t_1 =3.65, P<.001), while patients receiving 10 mg/d improved by

6.1±8.2 points (t_1 =2.80, P=.006). The 15-mg/d group was not statistically superior to placebo (olanzapine, 15 mg/d, mean change, -4.9±7.8; t_1 =1.17, P=.24). The proportion of patients exhibiting a response on the Core Total (\geq 50% reduction, baseline to end point) was significantly greater for the 5-mg/d (65.5%, 36/55; Fisher exact P=.005) and 10-mg/d (57.1%, 28/49; Fisher exact P=.04) olanzapine groups compared with placebo (35.6%, 16/45) but not for the 15-mg/d group (43.1%, 22/51; Fisher exact P=.53).

Visitwise analysis of the Core Total (**Figure 2**) showed a statistically significant treatment effect relative to placebo at week 2 for the 5-mg/d $(-4.1\pm7.6 \text{ vs} -1.6\pm7.7; t_1=2.64, P=.009)$ and 10-mg/d $(-3.6\pm6.4 \text{ vs} -1.6\pm7.7; t_1=2.40, P=.02)$ olanzapine groups. The 5-mg/d olanzapine group continued to improve significantly for the remainder of the 6-week study period. The 10-mg/d group showed increasing improvement significantly superior to placebo at weeks 2, 4, 5, and 6. The 15-mg/d group showed an improvement throughout the entire treatment period that was not significantly greater than placebo. Patients treated with 5 mg/d of olanzapine dem-



Figure 1. Progress of patients throughout the 6-week trial. Intervention was the administration of study drug or placebo. Following randomization, 1 patient (placebo group) did not receive study drug but was included in the intent-to-treat efficacy analyses. Patients were included in the analyses of change from baseline to end point if they had both a baseline score and at least 1 postbaseline score. Following randomization and intervention, 6 patients were excluded from efficacy analyses for the following reasons: no postbaseline score for the primary efficacy measure (n=2) and improperly administered Neuropsychiatric Inventory–Nursing Home version (n=4). A total of 200 patients were included in the primary efficacy analysis.

onstrated significantly greater improvement relative to placebo on nearly all secondary efficacy measures, while the 10-mg/d group demonstrated significant improvement on several measures (Table 2). The 5- and 10-mg/d olanzapine groups each had significantly greater mean score reductions compared with placebo on the Agitation/Aggression item $(-4.1\pm3.7 \text{ vs} -2.1\pm4.6, [t_1=2.50, P=.01] \text{ and } -3.9\pm4.2 \text{ vs} -2.1\pm4.6 [t_1=2.39, P=.02], respectively) and the Psychosis Total (Hallucinations and Delusions total) <math>(-3.6\pm5.6 \text{ vs} -1.6\pm7.3 [t_1=3.27, P=.001] \text{ and } -2.2\pm5.8 \text{ vs} -1.6\pm7.3 [t_1=2.11, P=.04], respectively).$

Improvement in noncognitive neuropsychiatric symptoms associated with olanzapine treatment had a positive impact on nursing facility caregivers. A statistically significant reduction in caregiver distress, measured by the sum of the Occupational Disruptiveness scores for Agitation/Aggression, Hallucinations, and Delusions (Core Disruptiveness) was seen for patients treated with 5 mg/d of olanzapine (-2.7 ± 3.2 vs -1.5 ± 3.5 ; $t_1=2.69$, P=.008). Caregivers of patients treated with 5 mg/d of olanzapine also had similar reductions in Occupational Disruptiveness associated with Anxiety, Appetite and Eating Disorders, Delusions, Depression/Dysphoria, and

Table 1. Baseline Patient Characteristics*

		Olanzapine		
Characteristic	Placebo	5 mg/d	10 mg/d	15 mg/d
No. of patients	47	56	50	53
Age, y				
Mean (SD)	81.4 (6.7)	82.9 (6.5)	83.6 (6.5)	83.0 (6.7)
Range	61-94	67-94	65-97	67-94
Sex, No. (%)				
Male	18 (38.3)	23 (41.1)	17 (34.0)	22 (41.5)
Female	29 (61.7)	33 (58.9)	33 (66.0)	31 (58.5)
Time from nursing home admission to visit 1, mean (SD), y	1.6 (1.5)	1.5 (1.2)	1.6 (1.6)	1.7 (1.7)
Time from first AD symptom to visit 1, mean (SD), v	4.5 (2.9)	4.3 (3.5)	5.2 (5.0)	5.3 (3.7)
Time from AD diagnosis to visit 1, mean (SD), y	2.2 (2.1)	1.6 (1.5)	2.7 (2.8)	2.4 (2.4)
MMSE baseline scores, mean (SD)	7.3 (6.3)	7.3 (6.5)	6.6 (6.7)	6.4 (6.7)

* No statistically significant differences were found among treatment groups. AD indicates Alzheimer disease; MMSE, Mini-Mental State Examination.

Measurement Scale	n	Baseline, Mean (SD)	Change, Mean (SD)†	Test Statistic (df)	P (vs Placebo)‡
NPI/NH Core Total§					
Placebo	45	14.8 (8.7)	-3.7 (10.3)		
Ulanzapine, mg/d	55	$14 \ 4 \ (7 \ 4)$	76(77)	2.65 (1)	< 001
10	49	14.4 (7.4)	-6.1 (8.2)	2 80 (1)	006
15	51	14.1 (7.5)	-4.9 (7.8)	1.17 (1)	.24
NPI/NH Occupational Disruptiveness		· · · ·	()		
Placebo	45	5.3 (3.4)	-1.5 (3.5)		
Ulanzapine, mg/d	55	51(22)	07(20)	2.60.(1)	008
10	49	5 0 (2 9)	-2.7 (3.2)	1.08(1)	28
15	51	5.7 (3.3)	-2.3 (3.4)	1.47 (1)	.14
NPI/NH Agitation/Aggression			()		
Placebo	45	7.4 (3.4)	-2.1 (4.6)		
Olanzapine, mg/d		0.4 (0.0)		0.50 (4)	04
5	55	8.4 (3.2)	-4.1 (3.7)	2.50 (1)	.01
10	49 52	0.4 (3.0) 7 0 (3 <i>1</i>)	-3.9 (4.2)	2.39(1)	.02
NPI/NH Psychosis Total¶	52	1.5 (0.4)	-0.1 (4.1)	0.00 (1)	.00
Placebo	45	7.4 (7.3)	-1.6 (7.3)		
Olanzapine, mg/d			()		
5	55	6.2 (6.3)	-3.6 (5.6)	3.27 (1)	.001
10	49	5.8 (5.7)	-2.2 (5.8)	2.11 (1)	.04
15 NPI/NH Hallucinations	51	6.2 (6.4)	-1.9 (5.3)	1.28 (1)	.20
Placeho	45	24(37)	0 0 (4 2)		
Olanzapine, mg/d	-10	2.4 (0.7)	0.0 (4.2)		
5	55	1.7 (3.2)	-0.7 (3.2)	2.74 (1)	.007
10	49	1.3 (3.0)	-0.2 (3.1)	2.00 (1)	.05
15	51	2.2 (3.8)	-0.7 (2.9)	1.66 (1)	.10
NPI/NH Delusions	45	4.0 (4.7)	1 C (4 D)		
Placebo Olanzanine mg/d	45	4.9 (4.7)	-1.0 (4.3)		
5	55	45(43)	-29(39)	2 52 (1)	01
10	49	4.4 (4.4)	-2.0 (4.2)	1.45 (1)	.15
15	52	4.0 (4.0)	–1.3 (3.3)	0.47 (1)	.64
NPI/NH Depression/Dysphoria					
Placebo	45	2.6 (3.4)	-1.0 (3.2)		
Ulanzapine, mg/d	55	2 8 (2 7)	20(27)	1 09 (1)	28
10	49	2.0 (3.7)	-2.0 (3.7)	0.00(1)	.20 > 99
15	51	2.2 (3.0)	-0.2 (3.8)	0.99 (1)	.32
NPI/NH Total		()			
Placebo	45	44.2 (24.3)	-10.4 (27.5)		
Olanzapine, mg/d		40 7 (00 0)	40 7 (04 0)	0.00 (4)	005
5	55	43.7 (23.0)	-18.7 (21.3)	2.89(1)	.005
10	49 51	40.7 (20.0) 41 0 (22 0)	-14.0 (21.7) -9.7 (26.1)	0.22 (1)	.09
BPRS Total	01	41.0 (22.0)	0.7 (20.1)	0.22 (1)	.00
Placebo	33	25.7 (8.4)	-1.4 (11.1)		
Olanzapine, mg/d		()	()		
5	40	30.9 (11.7)	-6.8 (8.6)	2.88 (1)	.005
10	37	26.0 (11.0)	-5.6 (10.0)	1.87 (1)	.06
10 RDRS Positive subscale#	39	30.0 (10.9)	-4.0 (10.9)	1.52 (1)	.13
Placebo	35	77(32)	-04(44)		
Olanzapine, mg/d		(012)	0.1 ()		
5	40	8.5 (4.6)	-2.0 (3.5)	1.93 (1)	.05
10	37	7.4 (3.9)	-1.4 (3.5)	0.84 (1)	.40
15	41	8.1 (4.9)	-1.4 (5.2)	1.44 (1)	.15
BPRS Anxiety/Depression subscale**	25	2 0 (2 0)	0 1 (2 6)		
Olanzanine mg/d	30	3.0 (3.2)	0.1 (3.0)		
oranzapino, my/u		5.0.(0.0)	10(00)	0.05 (4)	0.4
5	42	50(30)	-1.3 (3 ()	2 05 (1)	()4
5 10	42 39	5.0 (3.0) 4.2 (3.0)	-1.3 (3.0) -1.5 (2.5)	2.05 (1) 2.30 (1)	.04 .02

*NPI/NH indicates Neuropsychiatric Inventory-Nursing Home version; BPRS, Brief Psychiatric Rating Scale; and ellipses, not applicable. A manufactor with the properties of the providence of

¶Sum of NPI/NH Hallucinations and Delusions items scores. #Consists of Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Conceptual Thought Disorder.

** Consists of Somatic Concern, Anxiety, Guilt Feelings, and Depressive Mood.

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Figure 2. Visitwise results for the Neuropsychiatric Inventory–Nursing Home version (NPI/NH) Core Total score. The NPI/NH Core Total (sum of the Agitation/Aggression, Hallucinations, and Delusions items) scores across the 6-week study period for placebo and olanzapine groups (5, 10, and 15 mg/d). Patients treated with 5 mg/d of olanzapine showed a significantly greater improvement compared with placebo at week 2, which was maintained throughout the study. Patients treated with 10 mg/d of olanzapine showed a significantly greater improvement at week 2, which was maintained at weeks 4 to 6. Asterisk indicates P<.05 vs placebo; dagger, P<.01 vs placebo; and double dagger, P<.001 vs placebo.

Hallucinations items. Although the reduction in Occupational Disruptiveness for the 10-mg/d olanzapine group did not differ significantly from placebo, it also did not differ significantly from the 5-mg/d group.

Significantly greater improvement associated with 5 mg/d of olanzapine was evident in the BPRS Total (-6.8 ± 8.6 vs -1.4 ± 11.1 ; $t_1=2.88$, P=.005). The 5- and 10-mg/d olanzapine groups exhibited significantly greater improvement on the BPRS Anxiety/Depression subscale relative to placebo (-1.3 ± 3.0 vs $+0.1\pm3.6$ [$t_1=2.05$, P=.04] and -1.5 ± 2.5 vs $+0.1\pm3.6$ [$t_1=2.30$, P=.02], respectively). Changes in NPI/NH Depression/Dysphoria scores were not significantly different among any of the treatment groups; mean scores were low at baseline, and fewer than one third of patients experienced mood alterations. The MMSE scores of patients in the 3 olanzapine groups were not significantly different from baseline (mean change, 5 mg/d: 0.8 ± 3.9 ; 10 mg/d: -0.5 ± 3.3 ; 15 mg/d: -1.0 ± 3.1) or from placebo (mean change, -0.3 ± 2.2).

SAFETY RESULTS

There were no statistically significant mean changes in EPS, as measured by the Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale, or in the categorical analysis of treatmentemergent adverse events. The incidence of spontaneously reported EPS was low among the olanzapine groups: no EPS event (tremor, hypertonia, cogwheel rigidity, hyperkinesia, akathisia, dyskinesia, dystonia, extrapyramidal syndrome [parkinsonism], tardive dyskinesia) was statistically different from placebo.

Treatment-emergent adverse events represent signs and symptoms spontaneously identified clinically during the study and do not reflect formalized, objective, operationalized data collected by the efficacy measures. All olanzapine-emergent events were similar compared with placebo except somnolence and abnormal gait (**Table 3**). The olanzapine groups had significantly higher rates of somnolence than the placebo group, with 4 patients dis-

Table 3. Treatment-Emergent Adverse Events*

	Olanzapine		
Placebo (n = 47)	5 mg/d (n = 56)	10 mg/d (n = 50)	15 mg/d (n = 53)
13 (27.7)	14 (25.0)	12 (24.0)	20 (37.7)
3 (6.4)	14 (25.0)‡	13 (26.0)‡	19 (35.8)
5 (10.6)	8 (14.3)	6 (12.0)	13 (24.5)
1 (2.1)	11 (19.6)§	7 (14.0)	9 (17.0)‡
4 (8.5)	1 (1.8)	2 (4.0)	8 (15.1)
7 (14.9)	5 (8.9)	6 (12.0)	8 (15.1)
1 (2.1)	5 (8.9)	7 (14.0)	7 (13.2)
4 (8.5)	5 (8.9)	6 (12.0)	6 (11.3)
3 (6.4)	0 (0.0)	2 (4.0)	6 (11.3)
3 (6.4)	7 (12.5)	5 (10.0)	4 (7.5)
3 (6.4)	2 (3.6)	6 (12.0)	4 (7.5)
2 (4.3)	4 (7.1)	6 (12.0)	1 (1.9)
	Placebo (n = 47) 13 (27.7) 3 (6.4) 5 (10.6) 1 (2.1) 4 (8.5) 7 (14.9) 1 (2.1) 4 (8.5) 3 (6.4) 3 (6.4) 3 (6.4) 2 (4.3)	Placebo (n = 47) 5 mg/d (n = 56) 13 (27.7) 14 (25.0) 3 (6.4) 14 (25.0) $\frac{1}{5}$ (10.6) 3 (2.1) 14 (25.0) $\frac{1}{5}$ (10.6) 8 (14.3) 1 (2.1) 11 (19.6) $\frac{5}{5}$ (8.9) 1 (2.1) 7 (14.9) 5 (8.9) 1 (2.1) 5 (8.9) 1 (2.1) 5 (8.9) 3 (6.4) 0 (0.0) 3 (6.4) 7 (12.5) 3 (6.4) 2 (3.6) 2 (4.3) 4 (7.1)	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

*Data are presented as number (percentage) and include all treatment-emergent adverse events with an incidence \geq 10% or significantly greater than placebo, regardless of cause. No statistically significant differences occurred among treatment groups. COSTART indicates Coding Symbols for a Thesaurus for Adverse Reaction Terms.

+Accidental injury includes abrasion, bruise, cut or laceration, fall, fracture, and skin tear.

\$P<.05, relative to placebo (Fisher exact test).

§P< 01, relative to placebo (Fisher exact test).

||P<.001, relative to placebo (Fisher exact test).

continuing due to somnolence (olanzapine, 5 mg/d: 1; 10 mg/d: 0; 15 mg/d: 3). The risk of somnolence in the 5-, 10-, and 15-mg/d olanzapine groups was estimated to be 4.9, 5.2, and 8.2 times greater than in the placebo group, respectively. Within the olanzapine groups, 28.3% of patients who experienced somnolence also had abnormal gait, compared with 12.4% of patients without somnolence (Fisher exact P = .02). Results of an analysis of covariance controlling for somnolence showed no significant effect of somnolence on the primary efficacy results, and the treatment effects remained statistically significant. Treatment-emergent weight changes were not significantly greater than placebo for olanzapine. Weight loss occurred at an incidence of 10% or more (Table 3), whereas weight gain was 10% or less (placebo: 3 [6.4%]; olanzapine, 5 mg/d: 3 [5.4%]; olanzapine, 10 mg/d: 1 [2.0%]; olanzapine, 15 mg/d: 0 [0.0%]).

Patients treated with 5 or 15 mg/d of olanzapine had significantly higher rates of treatment-emergent abnormal gait (stooped posture, unsteady gait, leaning, ambulation dysfunction) than placebo-treated patients. The risk of abnormal gait in the 5-, 10-, and 15-mg/d olanzapine groups was estimated to be 11.2, 7.5, and 9.4 times greater than in the placebo group, respectively. Of the 28 patients reported to have treatment-emergent abnormal gait, 24 had Simpson-Angus Scale assessments. Of those 24 patients, the Gait item score worsened from baseline to end point for 7 patients (placebo: 1; olanzapine, 5 mg/d: 1; olanzapine, 10 mg/d: 1; olanzapine, 15 mg/d: 4). Post hoc analysis of the Simpson-Angus Gait item revealed no statistically significant differences for any olanzapine group compared with placebo in mean change from baseline to end point.

Anticholinergic effects were assessed by identifying reported classification terms from the Coding Symbols for a Thesaurus for Adverse Reaction Terms (COSTART) that potentially could be related to central or peripheral anticholinergic activity. (Central activity terms included agitation, confusion, delirium, delusions, dyskinesia, fever, hallucinations, thinking abnormal, and twitching. Peripheral activity terms included amblyopia, constipation, dry mouth, dry skin, fecal impaction, fever, intestinal obstruction, tachycardia, urinary retention, and vasodilation.) There were no significant differences in any olanzapine group for any of the individually listed central or peripheral COSTART terms compared with placebo. Pooling COSTART peripheral anticholinergic terms revealed a significant difference between the 15-mg/d olanzapine group and placebo (26.0% and 6.4%, respectively; Fisher exact P=.008). No significant differences were evident when central anticholinergic terms were pooled.

No clinically significant differences emerged between placebo and olanzapine groups for changes in vital signs, weight, or ECG measures. The incidence of clinically meaningful orthostatic hypotension (\geq 30 mm Hg decrease of systolic blood pressure, supine to sitting) was nearly identical for placebo patients (7.0%) and olanzapine patients (7.2%, Fisher exact P>.99). The effect of olanzapine on cardiac function was addressed in the analyses of mean change from baseline to end point and categorical changes for ECG heart rate and interval times (PR, QRS, QT, QTc). There were no statistically significant differences between any of the olanzapine groups and placebo.

COMMENT

In the present study, low-dose olanzapine (5 and 10 mg/d) was significantly superior to placebo and safe in treating behavioral and psychotic symptoms of patients with AD in nursing care facilities. Patients receiving these lower doses showed an approximate 50% mean improvement in NPI/NH Core Total scores, as identified by their caregivers, with clinical improvements corresponding to an average change from moderate severity or frequent symptoms to mild or infrequent. This is one of only a few controlled clinical trials demonstrating the efficacy and safety of atypical antipsychotics for behavioral and psychotic disturbances in elderly patients.

Two placebo-controlled, double-blind studies have been reported using the atypical antipsychotic risperidone. De Deyn et al²⁸ compared placebo and flexibledose (0.5-4 mg/d) risperidone or haloperidol for behavioral symptoms. The percentage of risperidone-treated (mean dose, 1.1 mg/d) and haloperidol-treated (mean dose, 1.2 mg/d) patients demonstrating clinical improvement (\geq 30% reduction from baseline to end point in BEHAVE-AD Total) was not significantly greater than placebo. Aggression scores were significantly improved relative to placebo for risperidone, and EPS were significantly higher in patients receiving haloperidol than risperidone or placebo. Katz et al²⁹ reported a large, placebo-controlled study of flexibledose risperidone (0.5-2.0 mg/d) for psychotic and behavioral symptoms. Doses of 1 or 2 mg/d were effective in reducing delusions and aggressiveness; the higher dose was associated with a greater incidence of EPS, somnolence, and peripheral edema.

To date, there have been no published placebocontrolled studies of quetiapine or clozapine in elderly demented patients. Clozapine, in small, open-label studies and retrospective case examinations, was reported effective for various psychotic disease states.³⁰⁻³² Confusion, sedation, and a higher risk of agranulocytosis in older patients were noted.^{33,34} Interim analysis of an openlabel trial of quetiapine fumarate in elderly patients suggested an improvement in the BPRS Total and Clinical Global Impressions of Severity of Illness scores.³⁵

In this study of olanzapine, the lowest dose (5 mg/d) appeared to have the greatest effect. Other atypical and conventional antipsychotics also are optimal at lower doses in elderly demented patients, usually due to decreased tolerability at higher doses (EPS, orthostatic hypotension, confusion).^{13,28,29,36} This is the first controlled study of an antipsychotic in an elderly demented population using a dose (15 mg/d) that is effective and tolerated in other psychotic disorders.^{14,37,38}

The inverse correlation of efficacy and olanzapine dose is potentially multifactorial. Age-related pharmacokinetic changes (absorption, distribution, metabolism, excretion of drugs)³⁹ and age-related (particularly >70 years)⁴⁰ pharmacodynamic alterations (end-organ receptor density and affinity, postreceptor response) influence dose and tolerability.^{41,42} These, coupled with the ongoing neuropathology of AD,⁴³ potentially contributed to the decreased drug response seen with the high dose in the present study.^{42,44} The 15-mg/d dose of olanzapine demonstrated a negative effect on tolerability and potentially affected efficacy.

Because of the reduction in cholinergic neurotransmission in AD, drugs with moderate-to-significant anticholinergic potential are avoided or used with caution.⁴⁵ Although the incidence of pooled anticholinergic peripheral effects was higher with 15 mg/d of olanzapine relative to placebo, central effects were not significantly different, including cognition. The MMSE scores in all 3 olanzapine groups were not significantly different from baseline or placebo. Olanzapine demonstrates a relatively high affinity for muscarinic receptors in preclinical in vitro binding assays using low-ionicstrength buffer.⁴⁶ However, in physiological binding medium, the affinity of olanzapine, but not atropine, was greatly reduced.⁴⁷ These latter data correlate with both ex vivo and in vivo studies that demonstrate that olanzapine has relatively minimal functional effects at muscarinic receptors.48-51

Olanzapine was generally well tolerated in this elderly population. Somnolence was dose related in the olanzapine treatment groups, and abnormal gait occurred at a statistically significantly higher incidence compared with placebo in the 5- and 15-mg/d groups. These data are of clinical significance in an elderly patient population potentially at risk for these events. Cardiovascular monitoring demonstrated no clinically significant effects, with no increases in incidence of orthostatic hypotension, arrhythmias, or QTc prolongation in any of the olanzapine groups compared with placebo. Objective EPS were absent with olanzapine use. This is particularly important because EPS occur with a higher incidence in geriatric patients with dementia, even in those previously unexposed to antipsychotics.^{52,53}

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Neuropsychiatric symptoms may have substantial impact on caregiver job satisfaction, and nursing facilities may have difficulty attracting and retaining caregiver staff. The beneficial effect of olanzapine, 5 mg/d, on Occupational Disruptiveness reflecting Core Disruptiveness (Agitation/Aggression, Hallucinations, and Delusions) and other behavioral items was significant.

Limitations of the present study include a duration too short to assess potential long-term antipsychotic effects, such as tardive dyskinesia. The study was not powered to detect infrequent adverse events between treatment groups or to stratify the results on sex or age, and the fixed dosing does not mirror clinical practice. Additional studies are needed to determine the benefit of olanzapine to noninstitutionalized patients, the long-term effects of treatment, the comparative safety and efficacy compared with other agents used in patients with AD, and the impact on quality-of-life scales and health economics.

In summary, this study indicates that low-dose olanzapine (5 and 10 mg/d) is effective in reducing behavioral disturbances and psychotic symptoms in patients with AD residing in nursing care facilities. The safety profile of low-dose olanzapine indicated it was well tolerated relative to placebo, including no significant cognitive decline during the 6 weeks of therapy.

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REFERENCES

- Borson S, Raskind MA. Clinical features and pharmacologic treatment of behavioral symptoms of Alzheimer's disease. *Neurology*. 1997;48(5 suppl 6):S17-S24.
- Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 1996;46:130-135.

- Patterson MD, Bolger JP. Assessment of behavioral symptoms in Alzheimer disease. Alzheimer Dis Assoc Disord. 1994;8(suppl 3):4-20.
- Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry.* 1987;48(suppl):9-15.
- Reisberg B, Ferris SH, de Leon MJ, Kluger A, Franssen E, Rorenstein J, Alba RC. The stage specific temporal course of Alzheimer's disease: functional and behavioral concomitants based upon cross-sectional and longitudinal observation. *Prog Clin Biol Res.* 1989;317:23-41.
- Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. Am J Psychiatry. 1989;146:577-587.
- Levy ML, Cummings JL, Fairbanks LA, Bravi D, Calvani M, Carta A. Longitudinal assessment of symptoms of depression, agitation and psychosis in 181 patients with Alzheimer's disease. Am J Psychiatry. 1996;153:1438-1443.
- Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias. Am J Geriatr Psychiatry. 2000;8:29-33.
- Nursing home attendants urged to report attacks by residents [news brief]. CMAJ. 1988;138:732.
- Everitt DE, Fields DR, Soumerai SS, Avorn J. Resident behavior and staff distress in the nursing home. J Am Geriatr Soc. 1991;39:792-798.
- Cowles CM. Nursing Home Statistical Yearbook. Anacortes, Wash: Cowles Research Group; 1997.
- Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc. 1990;38:553-563.
- Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, Cooper TB, Pelton GH, Mayeux R. A randomized, placebo-controlled dose-comparison trial of haloperidol for psychoses and disruptive behaviors in Alzheimer's disease. Am J Psychiatry. 1998;155:1512-1520.
- Beasley CM Jr, Tollefson GD, Tran PV. Efficacy of olanzapine: an overview of pivotal clinical trials. J Clin Psychiatry. 1997;58(suppl 10):7-12.
- Reams SG, Sanger TM, Beasley CM Jr. Olanzapine in the treatment of elderly patients with schizophrenia and related disorders. *Schizophr Res.* 1998;29:151-152.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
- Wood S, Cummings JL, Hsu MA, Barclay T, Wheatley MV, Yarema KT, Schnelle JF. The use of the neuropsychiatric inventory in nursing home residents: characterization and measurement. Am J Geriatr Psychiatry. 2000;8:75-83.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
- Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients by the clinician. *J Psychiatr Res.* 1975; 12:189-198.
- Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gorbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.
- Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, Mac-Millan A, Keleher P, Dekosky S. The impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. J Am Geriatr Soc. 1998;46:210-216.
- 22. Wood S, Cummings JL, Barclay T, Hsu MA, Allahyar M, Schnelle JF. Assessing

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the impact of neuropsychiatric symptoms on distress in professional caregivers. *Aging Mental Health.* 1999;3:241-245.

- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962; 10:799-812.
- Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand. 1970;212:S11-S19.
- Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154: 672-676.
- Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised Edition. Bethesda, Md: US Dept of Health, Education and Welfare; 1976.
- Gillings D, Koch G. The application of the principle of intention-to-treat to the analysis of clinical trials. *Drug Info J.* 1991;25:411-425.
- De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PLJ, Eriksson S, Lawlor BA. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. *Neurology*. 1999;53:946-955.
- Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry. 1999;60:107-115.
- Balle CJ. The use of clozapine in older people. Int J Geriatr Psychiatry. 1992;7: 689-692.
- Chengappa KN, Baker RW, Kreinbrook SB, Adair D. Clozapine use in female geriatric patients with psychoses. J Geriatr Psychiatry Neurol. 1995;8:12-15.
- Salzman C, Vaccaro B, Lieff J, Weiner A. Clozapine in older patients with psychosis and behavioral disturbances. *Am J Geriatr Psychiatry*. 1995;3:26-33.
- Frankenburg FR, Kalunian D. Clozapine in the elderly. J Geriatr Psychiatry Neurol. 1994;7:129-132.
- Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapineinduced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med.* 1993;329:162-167.
- McManus DQ, Arvanitis LA, Kowalcyk BB, and the Seroquel Trial 48 Study Group. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. J Clin Psychiatry. 1999;60:292-298.
- Devanand DP, Sackeim HA, Brown RP, Mayeux R. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. Arch Neurol. 1989;46:854-857.
- Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, Petty F, Centorrino F, Wang R, Grundy SL, Greaney MG, Jacobs TG, David SR, Toma V. Olanzapine versus placebo in the treatment of acute mania. *Am J Psychiatry*. 1999;156:702-709.
- Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley CM Jr, Tollefson GD. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol.* 1997;17:407-418.

- Triggs EJ, Nation RL. Pharmacokinetics in the aged: a review. J Pharmacokinet Biopharm. 1975;3:387-418.
- Vestal RE, Norris AH, Tobin JD, Cohen BH, Shock NW, Andres R. Antipyrine metabolism in man: influence of age, alcohol, caffeine and smoking. *Clin Pharmacol Ther.* 1975;18:425-432.
- Chutka DA, Evans JM, Fleming KC, Mikkelson KG. Drug prescribing for elderly patients. *Mayo Clin Proc.* 1988;70:685-693.
- 42. Roberts J, Turner N. Altered pharmacodynamic basis for altered drug action in the elderly. *Clin Geriatr Med.* 1988;4:127-149.
- Giannakopoulos P, Canuto A, Hof PR, Bouras C. Cerebral cortex pathology in aging and Alzheimer disease. In: Vellas B, Fitten LJ, eds. *Research and Practice* in Alzheimer Disease. New York, NY: Springer Publishing Co; 1999:55-60.
- Crooks J. Aging and drug disposition: pharmacodynamics. J Chronic Dis. 1983; 36:85-90.
- Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. *Neurology*. 1996;47:876-883.
- Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong TD. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology*. 1996;14:87-96.
- Bymaster FP, Falcone JF. Decreased binding affinity of olanzapine and clozapine for clonal human muscarinic receptor subtypes in intact CHO cells in physiological medium. *Eur J Pharmacol.* 2000;390:245-248.
- Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? a review of the evidence. *Neuropsychopharmacology*. 1998;18:63-101.
- Bymaster FP, Moore NA, Nakazawa T. Review of the preclinical pharmacology of olanzapine: a MARTA class antipsychotic. *Jpn J Clin Psychopharmacol.* 1999; 2:885-911.
- 50. Bymaster FP, Nelson DL, DeLapp NW, Falcone JF, Eckols K, Truex LL, Foreman MM, Lucaites VL, Calligaro DO. Antagonism by olanzapine of dopamine D1, serotonin₂, muscarinic, histamine H1 and α_1 -adrenergic receptors in vitro. *Schizophr Res.* 1999;37:107-122.
- Schotte A, Janssen PF, Gommeren W, Luyten WH, van Gompel P, Lesage AS, de Loore K, Leysen JE. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. *Psychopharmacology*. 1996; 124:57-73.
- Girling DM, Berrios GE. Extrapyramidal signs, primitive reflexes and frontal lobe function in senile dementia of the Alzheimer type. *Br J Psychiatry*. 1990;157: 888-893.
- 53. Sweet RA, Akil M, Mulsant BH, Ulrich R, Pasternak RE, Zubenko GS. Determinants of spontaneous extrapyramidal symptoms in elderly psychiatric inpatients diagnosed with Alzheimer's disease, major depressive disorders, or psychotic disorders. J Neuropsychiatry Clin Neurosci. 1998;10:68-77.