The Effects of Olanzapine in Reducing the Emergence of Psychosis Among Nursing Home Patients With Alzheimer's Disease

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Background: Elderly patients with Alzheimer's disease (AD) commonly exhibit psychotic symptoms, prompting clinicians to administer antipsychotics. This article compares the effects of olanzapine and placebo in the emergence of hallucinations or delusions in AD patients with symptoms of agitation/aggression but little or no psychotic symptomatology at baseline.

Method: A multicenter, double-blind, placebo-controlled study was conducted in nursing home patients with AD according to DSM-IV criteria and symptoms of agitation/aggression and/or psychosis. Patients (N = 206) were randomly assigned to receive either placebo or fixed-dose olanzapine (5, 10, or 15 mg/day) for up to 6 weeks. This article analyzes data from a subgroup of patients (N = 165) with no or minimal delusions and/or hallucinations at baseline as measured by the Neuropsychiatric Inventory-Nursing Home Version (NPI/NH). Three subsets of patients were identified on the basis of their symptoms at baseline: those with no clinically significant hallucinations, those with no clinically significant delusions, and those with no clinically significant delusions or hallucinations.

Results: Of the patients without hallucinations or delusions at baseline (N = 75), the placebo-treated patients showed significantly greater development of these symptoms compared with olanzapine-treated patients overall (NPI/NH hallucinations + delusions mean change score, +2.73 vs. +0.27, p = .006). Similarly, of the patients without baseline hallucinations (N = 153), the placebo-treated patients showed greater hallucinations score increases than did olanzapine-treated patients overall (+1.25 vs. +0.33, p = .026), whereas patients without baseline delusions (N = 87) showed no significant treatment effects. Olanzapine had a favorable safety profile in each patient subset.

Conclusion: These results suggest that, overall, olanzapine effectively attenuated emergence of psychosis in a short-term trial of patients with Alzheimer's disease.

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Approximately 2% to 5% of the population over 65 years of age and 20% of people over 80 years of age are afflicted with Alzheimer's disease (AD).[1,2] Of these, up to 50% may exhibit psychotic symptoms (hallucinations and delusions).[3] The presence of such symptoms in AD patients is associated with a more rapid cognitive decline[4] and is a major cause of patient institutionalization and caregiver distress.[3,5] The psychosis of AD tends to follow a "waxing and waning" course, and therefore, therapeutic interventions that attenuate the reemergence of psychotic symptoms may have a substantial impact on the quality of life of these patients. Classic neuroleptics such as haloperidol and thioridazine are commonly used to treat AD patients who exhibit psychotic symptoms, but these drugs have been only moderately effective in controlling psychotic symptoms.[6,7] Moreover, the use of typical antipsychotics is associated with a high incidence of extrapyramidal adverse reactions and other unwanted side effects.[7,8]

Olanzapine, an "atypical" antipsychotic, has demonstrated efficacy in treating schizophrenia,[9] schizoaffective disorder,[10] and acute mania,[11] with a favorable extrapyramidal symptom profile. This agent has also demonstrated usefulness in preventing relapse in patients with schizophrenia.[12] While olanzapine has been shown to be effective in treating psychosis, its effect in attenuating the emergence of psychosis has not previously been demonstrated in a population of exclusively elderly patients. We report here the results of an analysis of a multicenter study[13] that assessed the efficacy and safety of olanzapine in treating psychotic symptoms and behavioral disturbances associated with AD. This analysis was conducted to determine the efficacy of olanzapine versus placebo in attenuating the emergence of hallucinations or delusions in AD patients who were without clinically significant

levels of these features at baseline during a 6-week treatment period. On the basis of the antipsychotic efficacy of olanzapine that was seen in the parent study on which this analysis is based, we hypothesized that the use of olanzapine would be associated with a reduced emergence of psychotic symptoms relative to the incidence in placebo-treated patients.

METHOD

Patient Sample

Data were evaluated from nursing home patients who met the National Institute of Neurological and Communication Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria[14] for possible or probable AD or who met the criteria for dementia of the Alzheimer's type in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[15] The patients in this analysis were part of a larger group of 206 patients who exhibited psychotic symptoms or behavioral disturbances and were enrolled in a prospective, multicenter, double-blind study.[13] Patients in the larger group all had scores of 3 or greater on the agitation/aggression, hallucinations, or delusions items of the Neuropsychiatric Inventory-Nursing Home Version (NPI/NH)[16] (see Assessments). A score of 3 or greater correlates with a clinically significant level of psychotic or behavioral symptoms, corresponding with moderate severity or frequency. Patients were excluded from the study if they exhibited symptoms of delirium, had a Mini-Mental State Examination (MMSE)[17] score greater than 24 prior to study treatment, or had a history in the preceding 12 months of a DSM-IV Axis I disorder other than AD (schizophrenia, major depression, bipolar disorder, etc.). Patients were also excluded if they had any prior diagnosis of a serious neurologic condition other than AD that could contribute to psychosis or dementia, including Parkinson's disease, seizure disorder, and significant head trauma.

Patients in the current subgroup analyses were free of or had low levels of psychotic symptoms at baseline. Three subsets of patients were identified on the basis of their psychotic symptomatology: (1) those with no or minimal hallucinations at baseline ("no hallucinations"), (2) those with no or minimal delusions at baseline ("no delusions"), and (3) those with no or minimal hallucinations or delusions at baseline ("no psychotic symptoms"). These characterizations were made on the basis of a score of 2 or less on, respectively, the hallucinations item of the NPI/NH, the delusions item of the NPI/NH, or both. The threshold of 2 or less, referable to the protocol-defined inclusion criteria, represents a less than clinically significant level of psychotic symptoms. This level reflects mild, infrequent, or primarily nonexistent psychotic symptoms. These 3 subsets ("no hallucinations," "no delusions," and "no psychotic symptoms") were examined to assess whether hallucinations or delusions developed across the 6-week acute phase of this study.

Study Design

After a 3- to 14-day washout and placebo lead-in period, patients who met the criteria for enrollment were assigned by random allocation to 1 of 4 treatment groups in the 6-week, double-blind, acute therapy period of the study (study period 2): olanzapine, 5, 10, or 15 mg/day or placebo. Patients randomly assigned to the 10-mg/day and 15-mg/day treatment groups began treatment with 5 mg/day and had doses titrated to the target dose by an increase in 5-mg/day increments every 7 days. Patients could not decrease their dose and were discontinued from the study if they were unable to tolerate their assigned dose. Patients who completed study period 2 had the opportunity to continue into a third study period and receive open-label olanzapine for up to 18 weeks (data not reported).

Assessments

The NPI/NH,[16] Brief Psychiatric Rating Scale (BPRS),[18] and MMSE[17] were used to measure patients' psychiatric and cognitive states. The Neuropsychiatric Inventory (NPI)[19] evaluates psychopathology in patients with AD and other dementias. The nursing home version of the NPI consists of 10 behavioral items and 2 neurovegetative items, with the score of each item, if present, representing the product of symptom frequency (1 = occasionally to 4 = very frequently) multiplied by severity (1 = mild to 3 = severe). Responses are obtained by a trained interviewer from professional caregivers involved in the ongoing care of the patient in the previous week. Patients were evaluated at baseline and weekly for up to 6 weeks. For the current analyses, the primary evaluation was based on mean changes in the scores for the NPI/NH hallucinations and delusions items and the sum of the scores for the 2 items (psychosis total score).

Safety was assessed by evaluation of adverse events, akathisia, and extrapyramidal symptoms (EPS). Adverse events were collected by casual observation, nonprobing inquiry, and spontaneous report at each visit. EPS and akathisia were assessed with the Simpson-Angus Scale,[20] Abnormal Involuntary Movement Scale (AIMS),[21] and Barnes Akathisia Scale[22] at each regularly scheduled visit.

Statistical Methods

Standard descriptive statistics, including means, standard deviations, and ranges, were used to characterize the study subgroups. Patients were included in the analysis of change if they provided both a baseline and at least 1 postbaseline observation.[23] Assessments of treatment differences in the development of hallucinations, delusions, or both were carried out in 2 ways. First, mean changes from baseline to the last observed endpoint for the NPI/NH item scores were evaluated using an analysis of variance

Table 1. Patient Characteristics (N = 165)

Characteristic	No Psychotic Symptoms at Baseline (N = 75)	No Hallucinations at Baseline (N = 153)[a]	No Delusions at Baseline (N = 87)[b]
Age			
Mean ± SD, y	82.7 ± 6.7	83.2 ± 6.5	82.8 ± 6.6
Range, y	66–94	66–98	66–95
Gender, N (%)			
Female	39 (52.0)	91 (59.5)	45 (51.7)
Male	36 (48.0)	62 (40.5)	42 (48.3)
Racial origin, N (%)			
African descent	4 (5.3)	6 (3.9)	5 (5.7)
White	70 (93.3)	146 (95.4)	81 (93.1)
Hispanic	1 (1.3)	1 (0.7)	1 (1.1)

[a]Includes 78 patients who had delusions at baseline.
[b]Includes 12 patients who had hallucinations at baseline.

(ANOVA) model including terms for treatment, investigator, and the investigator-by-treatment interaction. Because of the relatively low rate of discontinuations in the overall patient population during the 6-week study period (54/206; 26.2%), little bias could be introduced by using the last observed measures. Model assumptions were assessed and deemed appropriate. Second, categorical assessment for the development of psychoses was defined as an NPI/NH item score of 3 or greater. Statistical comparisons of these proportions across treatment groups were based on the Fisher exact test. Both the model form for the continuous comparisons and the cutpoint for the categorical comparisons were defined in the protocol and planned for use prior to any of the post hoc analyses.

Because assessment of olanzapine treatment safety was not specific to any of the patient subsets studied, safety data are reported for the entire analysis subsample of patients. Baseline to last observed endpoint analysis of MMSE, Simpson-Angus Scale, AIMS, and Barnes Akathisia Scale scores was conducted using an ANOVA model with treatment, investigator, and treatment-by-investigator interaction terms. Categorical comparisons of treatment-emergent adverse events were carried out using the Fisher exact test. All cited p values were 2-tailed, with an α level of 0.05 defining statistical significance. Statistical Analysis Software[24] was used for all statistical analyses.

RESULTS

Patient and Illness Characteristics

A total of 165 patients from the original study were included in this analysis: 97 women and 68 men. The majority (95.2%) of patients were white. Patients' ages ranged from 66 to 98 years, with a mean age of 83.2 years. The olanzapine- and placebo-treated patient groups in each of the 3 illness categories ("no psychotic symptoms," "no hallucinations," and "no delusions") showed approximately equal compositions with respect to age, gender, and racial origin (Table 1). No significant baseline differences were found for these demographic characteristics across the 4 treatment groups (olanzapine, 5, 10, and 15 mg/day, and placebo).

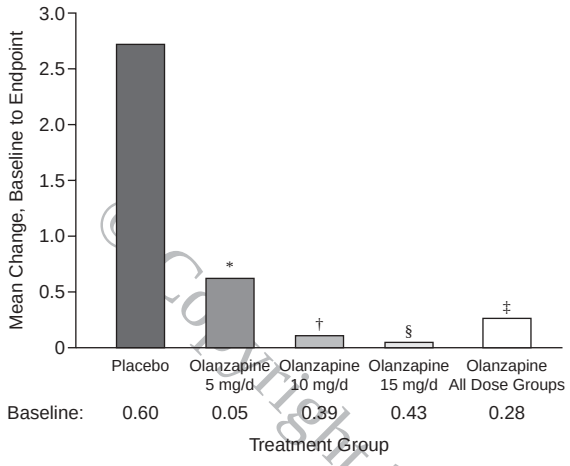
All patients within this subgroup analysis had exhibited behavioral disturbances at baseline in the form of agitation/aggression, with scores of 3 or greater on the NPI/NH agitation/aggression item. Patients who were characterized as having no or minimal hallucinations or delusions at baseline (the "no psychotic symptoms" subset of patients, N = 75) totaled 45.5% of the entire patient sample for this analysis (see Table 1). Most of these patients (83%; N = 62) had scores of 0 on both the hallucinations and delusions items of the NPI/NH. "No hallucinations" patients accounted for 153 (92.7%) of the 165 total patients in this subgroup analysis. The majority of these patients (88%) had a score of 0 on the NPI/NH hallucinations item at baseline. Of the 153 patients in the "no hallucinations" group, 78 exhibited some delusory symptoms, and the remaining 75 formed the "no psychotic symptoms" subset of patients. Within the overall group of 165 patients, 87 patients (52.7%) had no or minimal delusory symptoms at baseline. Most of these patients (89%) had a score of 0 on the NPI/NH delusions item at baseline. Twelve of the 87 patients had experienced some hallucinatory symptoms, and the remaining 75 patients again formed the "no psychotic symptoms" subset of patients.

Efficacy Analysis: Patients Without Psychoses at Baseline

The emergence of psychotic symptoms was measured with the NPI/NH psychosis total score, consisting of the sum of the hallucinations and delusions items of the NPI/NH. As illustrated in Figure 1, "no psychotic symptoms" patients who received placebo experienced a significantly greater increase in psychotic symptoms over the course of this 6-week study than did "no psychotic symptoms" patients overall who received olanzapine (placebo, 2.73 ± 4.53; olanzapine [all dosage groups] 0.27 ± 1.30; p = .006). This difference was most apparent at the higher doses of olanzapine (10 mg/day, p = .017; 15 mg/day; p = .005). The 5-mg/day dose also resulted in lower psychosis total scores than did placebo, but this difference in treatment effects did not reach statistical significance (Fisher exact p = .067).

Inspection of the baseline-to-endpoint score changes of the NPI/NH hallucinations and delusions items revealed that olanzapine had a similar effect in reducing the emergence of delusions and hallucinations, but only the change in the delusions item scores achieved statistical significance. Placebo-treated "no psychotic symptoms" patients experienced increases in their NPI/NH delusions item scores. In contrast, olanzapine-treated "no psychotic symptoms" patients overall showed no change from baseline. This treatment difference was significant

Figure 1. Change in Neuropsychiatric Inventory-Nursing Home Version Psychosis Total Score in Patients With No or Minimal Hallucinations and Delusions at Baseline



*p = .067 vs. placebo.
†p = .017 vs. placebo.
‡p = .006 vs. placebo.
§p = .005 vs. placebo.

(placebo, 1.13 ± 2.47; olanzapine [all dosage groups], 0.00 ± 0.64; p = .017). "No psychotic symptoms" patients who received olanzapine similarly experienced far fewer hallucinations overall than did such patients who received placebo, but this difference did not achieve statistical significance (placebo, 1.60 ± 2.92; olanzapine [all dosage groups], 0.27 ± 1.12; p = .073).

Efficacy Analysis: Patients Without Hallucinations at Baseline

As a secondary measure, the mean change in scores on the NPI/NH hallucinations item was studied in "no hallucinations" patients regardless of whether they exhibited delusional symptoms at baseline. As indicated in Table 2, "no hallucinations" patients receiving placebo experienced more hallucinations than did patients overall who received olanzapine (placebo, 1.25 ± 2.81; olanzapine [all dosage groups], 0.33 ± 1.25; p = .026).

Efficacy Analysis: Patients Without Delusions at Baseline

To determine the emergence of delusory symptoms, the mean change in scores on the NPI/NH delusions item was examined in "no delusions" patients (Table 3). Patients receiving placebo experienced an appearance of more delusional symptoms than did patients overall who received olanzapine. However, this treatment difference was not statistically significant (placebo, 0.94 ± 2.29; olanzapine [all dosage groups], 0.19 ± 1.45; p = .153), since less development of these symptoms occurred across all treatment groups.

Table 2. Mean Change in Neuropsychiatric Inventory-Nursing Home Version Hallucinations Item Scores From Baseline to Endpoint Among All Patients Without Hallucinations at Baseline

	Baseline		Change		p Value
Therapy	Mean	SD	Mean	SD	vs Placebo
Placebo (N = 32)	0.34	0.75	1.25	2.81	...
Olanzapine, 5 mg/d (N = 42)	0.07	0.26	0.50	1.31	.113
Olanzapine, 10 mg/d (N = 41)	0.20	0.51	0.29	1.42	.050
Olanzapine, 15 mg/d (N = 38)	0.16	0.49	0.18	0.95	.033
Olanzapine, all dose groups (N = 121)	0.14	0.43	0.33	1.25	.026

Table 3. Mean Change in Neuropsychiatric Inventory-Nursing Home Version Delusions Item Scores From Baseline to Endpoint Among All Patients Without Delusions at Baseline

	Baseline		Change		p Value
Therapy	Mean	SD	Mean	SD	vs Placebo
Placebo (N = 18)	0.22	0.55	0.94	2.29	...
Olanzapine, 5 mg/d (N = 23)	0.00	0.00	0.13	0.46	.169
Olanzapine, 10 mg/d (N = 21)	0.14	0.48	0.38	1.47	.435
Olanzapine, 15 mg/d (N = 25)	0.32	0.69	0.08	1.98	.174
Olanzapine, all dose groups (N = 69)	0.16	0.50	0.19	1.45	.153

Categorical Analysis

The appearance of clinically significant psychotic symptoms (NPI/NH item score ≥ 3) was lower in the olanzapine treatment groups than in the corresponding placebo treatment group (Table 4). This could be seen not only in analysis of olanzapine-treated patients overall, but also in the individual treatment groups (5, 10, and 15 mg/day). In the placebo group, 25% of patients (4 of 16) in the "no psychotic symptoms" subset went on to develop hallucinations and/or delusions, whereas 8.3% of the olanzapine-treated patients overall (5 of 60) developed psychotic symptoms (Fisher exact p = .087). In the "no hallucinations" subset, 21.9% of patients receiving placebo (7 of 32) experienced hallucinations, whereas 7.4% of the olanzapine-treated patients overall (9 of 121) experienced hallucinations. This treatment difference was significant (Fisher exact p = .045). In the "no delusions" subsample, 16.7% of placebo-treated patients (3 of 18) experienced delusions, compared with 4.3% of olanzapine-treated patients (3 of 69) (Fisher exact p = .100).

Safety Analysis

No significant differences were seen among treatment groups in patients' MMSE[17] baseline or change scores for any of the 3 illness subsets. Similarly, as measured by the Simpson-Angus Scale,[20] AIMS,[21] and Barnes Akathisia Scale,[22] EPS did not differ significantly at either baseline

Table 4. Categorical Summary: Number of Patients With Symptoms at Endpoint and Total Number of Patients Without Symptoms at Baseline

	Placebo			Olanzapine, 5 mg/d			Olanzapine, 10 mg/d			Olanzapine, 15 mg/d			All Olanzapine Dosage Groups		
Baseline Status	Patients With Symptoms at Endpoint	Total Patients Without Symptoms at Baseline	%	Patients With Symptoms at Endpoint	Total Patients Without Symptoms at Baseline	%	Patients With Symptoms at Endpoint	Total Patients Without Symptoms at Baseline	%	Patients With Symptoms at Endpoint	Total Patients Without Symptoms at Baseline	%	Patients With Symptoms at Endpoint	Total Patients Without Symptoms at Baseline	%
No psychotic symptoms	4	16	25.0	2	21	9.5	1	18	5.6	2	21	9.5	5	60	8.3
No hallucinations	7	32	21.9	4	42	9.5	3	41	7.3	2	38	5.3	9	121	7.4*
No delusions	3	18	16.7	0	23	0.0	2	21	9.5	1	25	4.0	3	69	4.3

*p = .045 vs. placebo, Fisher exact test.

or endpoint among patients categorized by treatment group. "Abnormal gait," a term from Coding Symbols for Thesaurus of Adverse Reaction Terms comprising "leaning," "limp," "stooped posture," and "unsteady gait," was reported at a higher incidence among olanzapine-treated patients than placebo-treated patients at the 5-mg/day and 15-mg/day doses (placebo, 0/33 [0.0%]; 5 mg/day, 6/37 [16.2%], Fisher exact p = .026; 15 mg/day, 8/35 [22.9%], Fisher exact p = .005). Somnolence, too, was reported at higher rates in the 10-mg/day and 15-mg/day groups, in a roughly dose-dependent manner (placebo, 3/33 [9.1%]; 10 mg/day, 13/39 [33.3%], Fisher exact p = .021; 15 mg/day 14/35 [40.0%], Fisher exact p = .005).

DISCUSSION

The results of these post hoc analyses indicate that, overall, olanzapine was effective in decreasing the emergence of psychotic symptoms in patients with AD who were relatively free of these symptoms at baseline. Previous studies have demonstrated that olanzapine is effective in reducing psychotic symptoms in schizophrenia, acute mania, and AD.[10,11,25] Moreover, in a recent report,[12] olanzapine was shown to prevent relapse of psychosis in stable schizophrenic patients, suggesting it may have a prophylactic effect as well as an ameliorative effect on psychosis. This study is the first to suggest that olanzapine may effectively attenuate the emergence of acute psychosis in patients with AD.

One constraint on our ability to interpret the data from the current analysis arises from the absence of historical data regarding patients' preexisting psychosis. It was unclear if patients who developed psychotic symptoms during this study were experiencing an exacerbation of a preexisting psychosis (i.e., they were in relative remission at baseline) or were experiencing a new onset of psychosis. This issue is particularly difficult to discern because of the natural "waxing and waning" course of psychosis in patients with AD. The results of this analysis appear to indicate an emergence rate for psychotic symptoms of 25% over a 6-week period among placebo-treated patients who were free of or had low levels of such symptoms at baseline. This high rate should not be interpreted as an incidence rate, because these patients simply crossed a threshold on a symptom scale, rather than having a clinical diagnosis related to their psychoses. Using these thresholds and measuring mean changes from the NPI/NH scale allow a greater statistical sensitivity to the emergence of psychotic symptoms and corresponding comparisons between treatment groups. Longitudinal studies typically indicate an overall emergence rate for psychotic symptoms in AD of between 40% and 80% over several years.[4,26,27] Little is available in the literature to indicate the rate of emergence of psychotic symptoms in elderly dementia patients over the short term, although De Deyn et al.[28] reported no statistically significant increase in either delusions or hallucinations over the 13 weeks of their study comparing risperidone, haloperidol, and placebo. Nevertheless, patients in the current analysis had concomitant agitation, and previous data indicate a high correlation between agitation that warrants pharmacologic intervention and the emergence of psychotic symptoms such as hallucinations.[3]

One drawback of the current study is its short duration. Although the olanzapine-treated group demonstrated an attenuation of psychotic symptoms relative to the placebo group, these findings must be regarded as tentative, and a prospective, long-term study involving larger treatment groups will be needed to verify the results that have been obtained. The finding that, overall, treatment with olanzapine resulted in an emergence of psychotic symptoms that was less than one third of that seen in the placebo-treated group is nevertheless instructive, since current thought suggests that early intervention, such as the cautious use of pharmacotherapy, can considerably improve the clinical outcome of patients who have already begun to exhibit psychotic symptoms.[29–31]

The effect pattern seen here for the 3 doses of olanzapine was not consistent with the efficacy results in the overall study. The parent study[13] found the 5-mg/day dose to be not only the most efficacious in reducing psychotic symptoms but also the safest. The 10-mg/day dose also demonstrated significant efficacy for olanzapine relative to placebo, but the results were less robust. The 15-mg/day

dose group failed to separate from the placebo group in their expression of psychotic symptoms and had a less tolerated safety profile. In contrast, the results here indicate a level attenuation of the emergence of psychosis across the 3 olanzapine doses, with a tendency toward greater effects at the higher doses. The sample size and short duration of this study are limitations that do not allow powerful comparisons among olanzapine doses. Given the safety and efficacy results from the parent study in combination with the findings here, 5 mg/day of olanzapine would be the most appropriate target dose for further study on reducing the emergence of psychosis in dementia.

The underlying pathology in AD has long been hypothesized to involve degeneration of central cholinergic systems.[30–34] Accordingly, patients with AD are at particular risk of the anticholinergic properties of antipsychotics. Olanzapine has an in vitro binding profile, suggesting that it is a potent antagonist of muscarinic receptors.[35] However, the compound has an activity in vivo at central cholinergic receptors that appears to be considerably less than is seen in vitro.[36,37] Use of olanzapine by the patients studied in the present analysis did not significantly affect their MMSE scores, indicating little, if any, effect on cognitive state after 6 weeks of treatment. This is consistent with preclinical findings with this compound.[38]

Care of patients with dementia is greatly complicated by their display of psychotic symptoms. This situation results in considerable distress among caregivers, affecting overall patient management and introducing difficulties concerning treatment strategy. For the patient, quality of life deteriorates to a greater extent, as paranoid delusions lead to bitterness, depression, and hostility.[3] Psychotic symptoms are associated with more rapid cognitive decline and increased severity of dementia.[4] It has been suggested that even a modest improvement in patients' psychotic symptomatology can lead to substantial improvements in their ability to function and decreases the likelihood of institutionalization.[39,40] It is therefore imperative that steps be taken toward the therapeutic amelioration of psychotic symptoms in patients with dementia.

In conclusion, patients with possible AD, concurrent behavioral symptoms of agitation/aggression, and no or minimal hallucinations and/or delusions experienced an overall significantly lower emergence of psychotic symptoms while receiving olanzapine, compared with placebo. These efficacy findings must be regarded initially as preliminary, as they remain to be replicated in studies that rely on longer treatment periods, larger sample sizes, different assessment scales, or a more varied patient sample. No statistically or clinically significant changes in cognitive state, EPS, or vital signs were seen, although significant increases in somnolence, abnormal gait, and nervousness were obtained.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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