Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia

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SUMMARY

Background   Psychotic symptoms and behavioral disturbances are a leading cause of institutionalization in elderly patients with Alzheimer's disease (AD).

Objectives   Elderly nursing home patients ($n = 105$) with possible or probable AD were entered into a multicenter study to determine the long-term efficacy and safety of olanzapine in treatment of psychotic symptoms and behavioral disturbances due to AD.

Methods   Following a double-blind, 6-week exposure to fixed-dose olanzapine (5, 10, or 15 mg/d), patients entered an additional 18-week, open-label, flexible-dose treatment. Baseline was defined from the start of the extension phase.

Results   Patients improved significantly on the primary efficacy measure, defined *a priori*, which consisted of the sum of the *Agitation/Aggression, Delusions*, and *Hallucinations* items ('Core') of the NPI/NH. Olanzapine also significantly improved scores for the NPI/NH total and the Core item-associated Occupational Disruptiveness of the NPI/NH, as well as the BPRS total and CGI Severity-of-Alzheimer's scores. Barnes Akathasia scores improved significantly from baseline, while Simpson-Angus and AIMS scores were not significantly changed. Treatment-emergent symptoms included somnolence, accidental injury, and rash. No significant changes were seen in ECGs, including QT_c interval, nor in weight or vital signs, including orthostasis.

Conclusions   Low-dose olanzapine appears to be effective and well tolerated for treatment of behavioral disturbances and psychotic symptoms due to AD in elderly patients. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; dementia; elderly; Neuropsychiatric Inventory; nursing home; olanzapine; psychosis

INTRODUCTION

Dementia is a common disorder of old age which affects an estimated 20% of all people aged 80 and older (Gurland and Cross, 1982). Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for 50–60% of all dementias in the elderly (Tomlinson *et al.*, 1970; Schoenberg *et al.*, 1987) Often accompanying the cognitive and functional decline and the progressive memory impairment that typifies AD is an increased incidence of behavioral disturbances, such as agitation, wandering, and violent verbal or physical outbursts, and the appearance of psychotic symptoms, particularly delusions and visual hallucinations. Behavioral disturbances represent the foremost patient-management problem in nursing homes (Cohen-Mansfield, 1986), and the severity of these disturbances has been found to correlate with patients' levels of cognitive impairment (Lloyd *et al.*, 1995). Estimates of the prevalence of psychotic features in dementia range from 15% to 75% (Devanand *et al.*, 1997; Drevets and Rubin, 1989), and their presence is associated with a more rapid cognitive decline (Rosen and Zubenko, 1991). Moreover, Jeste and Finkel (2000) suggest that patients' inability to articulate their delusions and hallucinations during advanced stages of dementia may

lead to an underestimate of the true incidence of psychosis. The appearance of neuropsychiatric disturbances has a major impact on patient management, causing distress to caregivers and affecting both the quality of patient care and the choice of treatment (Everitt *et al.*, 1991).

Treatment strategies for the control of behavioral disturbances and psychotic symptoms due to AD have included the use of anxiolytics, antidepressants, anticonvulsants, and antipsychotics. The vast majority of studies concerning the efficacy of antipsychotics in controlling neuropsychiatric symptoms due to AD have involved classical neuroleptics such as haloperidol and thioridazine. These have been found to be somewhat effective in controlling psychosis, anxiety, and agitation in some, but not all, investigations (Barnes *et al.*, 1982; Finkel *et al.*, 1995; Devanand *et al.*, 1998). A meta-analysis by Schneider *et al.* (1990) revealed that the treatment effect of the typical neuroleptics was slight, with no one agent better than another. Use of typical antipsychotics results in significant relapse (Frenchman and Prince, 1997), and is associated with high levels of toxicity, particularly in the form of extrapyramidal symptoms (EPS) (Barnes *et al.*, 1982; Auchus and Bissey-Black, 1997; Devanand *et al.*, 1998). Such problems tend to be less common among patients treated with the atypical antipsychotics. These drugs appear to hold much promise, significantly reducing behavioral and psychotic symptoms while demonstrating low levels of treatment failure and, with few exceptions (Breier *et al.*, 1999; Conley, 2000) having minimal propensity toward EPS and prolactin elevation (Frenchman and Prince, 1997; Solomons and Geiger, 1999).

Olanzapine, an atypical antipsychotic, has been demonstrated previously to be highly effective and well tolerated in the treatment of schizophrenia (Beasley *et al.*, 1996) and acute mania (Tohen *et al.*, 1999) and has a favorable EPS profile (Tollefson *et al.*, 1997; Tran *et al.*, 1997), which is of particular importance in treating elderly patients. The present study is an extension of a controlled, randomized, double-blind, fixed-dose, six-week study (Street *et al.*, 2000), which demonstrated that low doses of olanzapine (5 or 10 mg/d) were effective in reducing the severity of behavioral disturbances and psychotic symptoms due to AD in elderly nursing home patients. Low-dose olanzapine was found to be safe and relatively well tolerated. The objective of the present study was to assess the efficacy and safety of olanzapine over a longer period in controlling behavioral disturbances and psychotic symptoms among geriatric patients in a nursing home setting.

METHODS

Patient population

Patients were male and female nursing care facility residents 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 (McKhann *et al.*, 1984). For inclusion in the study, patients must have scored ≥ 3 on any of the *Agitation/Aggression*, *Hallucinations*, or *Delusions* items of the NPI/NH at initial screening and following a single-blind, placebo lead-in. Patients with a history of a (DSM-IV) Axis I disorder other than AD (APA, 1994) (for example, schizophrenia, bipolar disorder, or severe/recurrent depression) within the 12 months prior to Visit 1, and patients with any diagnosis of a serious neurological condition other than AD that could contribute to psychosis or dementia, were excluded from the study. An informed consent document approved by the institutional review board of each study center was signed by all patients and/or their designated representative prior to participation. Patients with a Mini-Mental State Exam (MMSE) (Folstein *et al.*, 1975) score greater than 24 were excluded, as were bedridden patients.

Study design

The trial period was an open-label extension phase, lasting up to 18 weeks, which followed a six-week randomized, double-blind, placebo-controlled study (Street *et al.*, 2000) conducted at 28 centers. This analysis focuses on patients ($n = 105$) who had received fixed doses of olanzapine (5, 10, 15 mg/d) during the preceding double-blind phase. Patients who met the criteria for enrollment and who completed the acute treatment period were eligible to enter this open-label extension phase, during which they received olanzapine in a flexible dose range of 5, 10, or 15 mg/d. Regardless of which treatment group they were in during the acute phase, all patients began open-label therapy with 5 mg of olanzapine (one tablet) daily, dispensed by the study site. Based on clinicians' judgment, subsequent daily doses were adjusted by one-tablet increments within the allowed dose range of 5–15 mg/d, with dosage increases permitted every seven days. Dose decreases were permitted at any time, but patients unable to tolerate the minimum dose of 5 mg/d were discontinued from the study.

Use of concomitant medications with primarily central nervous system activity was exclusionary—anticholinergic agents, cholinesterase inhibitors,

anticonvulsants, mood stabilizers, and tricyclic anti-depressants were not permitted. Unrestricted benzodiazepines were allowed during the open-label phase of the study.

Efficacy assessment

The Neuropsychiatric Inventory—Nursing Home version (NPI/NH) evaluates psychopathology in patients with AD and other dementias, and was developed for use in nursing facilities (Cummings *et al.*, 1994). Responses are obtained by a trained interviewer from informed caregivers involved in the ongoing care of the patient, and are based on observations made in the previous week. The NPI/NH consists of ten behavioral and two 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). For each item, an Occupational Disruptiveness score was also obtained. Occupational Disruptiveness takes into account the work, effort, time, or distress that a particular behavior causes the staff caregiver (0 = no disruption to 5 = very severe or extreme).

Baselines for this open-label extension were taken at the completion of the acute phase (Week 6). Efficacy measures are therefore expressed herein in terms of the additional improvement seen in patients after having already been treated for 6 weeks. All measures reported herein were defined *a priori*. The primary efficacy measure consisted of the mean change from baseline to endpoint in the sum of the *Agitation/ Aggression*, *Hallucinations*, and *Delusions* items of the NPI/NH scale (NPI/NH Core Total, range: 0–36). The NPI/NH Core Total was used to define patients as either responders (≥ 50% reduction from baseline) or nonresponders. Secondary efficacy measures included mean change from baseline to endpoint on the NPI/NH total score, an NPI/NH two-item total for *Hallucinations* and *Delusions* (Psychosis Total), NPI/NH individual items scores, and a combined NPI/NH Occupational Disruptiveness score for *Agitation/Aggression*, *Hallucinations*, and *Delusions* (NPI/NH Core Disruptiveness). The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) total, positive symptom cluster (Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, Unusual Thought Content), and subscale scores; the MMSE (Folstein *et al.*, 1975) total, and Clinical Global Impressions (CGI) (Guy, 1976) Severity of Psychosis and Behavior and Severity of Alzheimer's Disease scores were also used to

measure changes in symptomatology. Patients were assessed for efficacy of olanzapine at the beginning of the extension period and at the ends of Weeks 1, 2, 3, 4, 6, 10, 14, and 18 for the CGI-S. NPI/NH scores were taken only at baseline and at endpoint.

Safety assessment

Three scales were used to assess EPS, the Simpson–Angus Scale (Simpson and Angus, 1970), the Barnes Akathisia Scale (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976). At the start of the acute phase, medical history had been recorded, and psychiatric assessment, physical examination, and electrocardiography (ECG) had been performed. The physical examination and ECG were repeated at endpoint. Assessment of vital signs (lying and sitting blood pressure, pulse, weight, and temperature) and clinical laboratory testing (clinical chemistry, electrolytes, and hematology) were performed.

For categorical safety data, reporting for the open-label phase depended on prior history. If a patient experienced a first-time occurrence of an adverse event during this phase of the study, it is reported here in the description of open-label phase data. If, on the other hand, a patient experienced an adverse event during the acute phase of this study (Street *et al.*, 2000), it is reported here only if it worsened in severity during the open-label phase.

Safety was assessed weekly throughout the study and upon discontinuation. Extrapyramidal symptoms were assessed at the beginning of the open-label phase, at the end of Week 6, and at endpoint. Laboratory tests were taken at the beginning of the extension period, at the ends of Weeks 1, 3, 6, 10, 14, and at endpoint.

Statistical methods

Primary analyses were performed on an intent-to-treat basis, as defined by Gillings and Koch (1991). All hypotheses were tested using a two-sided α level of 0.05. Patients with a baseline and at least one postbaseline measurement were included in the analyses of change scores. Mean change from baseline to endpoint was tested for significance using a last-observation-carried-forward (LOCF) Student's *t* test. Secondary efficacy variables were analyzed using Student's *t* test described for the primary efficacy measure. Additionally, descriptive statistics were used to summarize categorical analysis of the percentage of responders (≥ 50% reduction from baseline to

endpoint). Analyses of continuous measures of safety (laboratory analytes, vital signs, EPS scales, and ECG intervals, including PR, QRS, QT, and corrected QT) were performed using LOCF Student's t test. Categorical analyses of laboratory values, vital signs, and ECG parameters, as well as treatment-emergent adverse events, were summarized using descriptive statistics. All p values are two-sided, and t statistics are given as absolute values.

RESULTS

Patient characteristics and disposition

A total of 105 patients were entered into this 18-week, open-label extension (see Table 1), comprising 67 females (64%) and 38 males (36%). Patients had a mean age of 83.4 years, with a range of 66 to 98 years. The majority (92%) were Caucasian. The mean baseline MMSE score ($n = 89$) was 7.0 (see Table 2), indicating severe cognitive impairment. Average time from onset of first definitive symptom of AD to the start of the acute phase of this study was 4.5 years (see Table 1), and average time since AD diagnosis was 2.1 years. Patients had been resident in their nursing home facilities an average of 1.4 years.

Seventy patients (67%) completed the entire 18-week study. Of the 35 patients who discontinued, 21 withdrew due to adverse events. No patients withdrew due to lack of efficacy. Total patient–days of exposure to olanzapine during this study was 10 853, with a

Table 1. Patient characteristics

Variable	Value
Number	105
Age: Years	
Mean (SD)	83.4 (6.6)
Range	66–98
Gender: n (%)	
Female	67 (63.8)
Male	38 (36.2)
Race: n (%)	
African descent	7 (6.7)
Caucasian	97 (92.4)
Hispanic	1 (1.0)
Time since first AD symptom ($n = 101$): Years	
Mean (SD)	4.5 (3.5)
Range	0.6–25.4
Time since diagnosis ($n = 103$): Years	
Mean (SD)	2.1 (1.8)
Range	0.003–8.3
Time since nursing home admission ($n = 104$): Years	
Mean	1.4 (1.2)
Range	0.04–4.8

mean exposure duration of 103 days and an overall mean modal dose of 7.0 mg/d. The modal dose (the dose that a patient was prescribed for the most number of days) for 66.7% of patients was 5 mg/d, while 10 mg/d was the modal daily dose for 21.0% of patients and 15 mg/d for 9.5%. The remaining 2.9% of patients for whom the modal daily dose was 0 mg/d, are included in this analysis based on the principle of intent to treat. Among patients using benzodiazepines ($n = 36$ patients), mean daily dose prorated for the entire study period, in lorazepam equivalents, was 0.09 mg/d. The olanzapine-treatment compliance rate, defined as the mean percentage of days that patients took the prescribed amount, was 96.1%.

Efficacy results

Over the course of the extension treatment period, olanzapine continued to decrease patients' levels of behavioral disturbances and psychotic symptoms (see Table 2), significantly reducing their mean NPI/NH Core Total (sum of the *Agitation/Aggression*, *Hallucinations*, and *Delusions* item scores) from a baseline score of 7.9 to an endpoint score of 6.0 ($t = 3.14$, $n = 91$, $p = .002$). Patients' improvement was also reflected in the changes in their mean scores for the *Agitation/Aggression* (-1.2 ± 3.5, $t = 3.28$, $n = 91$, $p = .001$) and *Delusions* (-0.6 ± 2.4, $t = 2.30$, $n = 91$, $p = .024$) items that make up a portion of the Core Total. *Anxiety*, *Disinhibition*, and *Irritability* were also significantly improved (see Table 2). The *Hallucinations* item, however, was not changed significantly further from the end of the acute treatment phase (-0.1 ± 1.7, $t = 1.71$, $n = 91$, $p = .428$). Nevertheless, NPI/NH Occupational Disruptiveness scores associated with the items of the Core Total continued to show significant improvement, decreasing from a mean baseline score of 3.0 to an endpoint score of 2.3 ($t = 3.03$, $n = 91$, $p = .003$). The percentage of patients responding to further treatment, defined as a 50% or greater additional reduction in Core Total score from the beginning of the extension phase, was 47.6%.

Other secondary measures of efficacy also reflected the continued improvements experienced by patients receiving olanzapine, including the NPI/NH total, the BPRS total, and the CGI Severity of Alzheimer's Disease score (see Table 2). However, BPRS negative and positive symptomatology and CGI Severity of Psychosis scores were not significantly changed from the end of the acute phase. Likewise, MMSE total

Table 2.   Summary of efficacy results

Measurement scale	n^a	Baseline[b] mean (SD)	Change[c] mean (SD)	t Statistic (abs value)	p Value[d]
NPI/NH Core Total[e]	91	7.9 (7.0)	− 1.9 (5.8)	3.14	.002
Total	91	27.9 (25.3)	− 6.2 (17.2)	3.44	< .001
Psychosis Total[f]	91	3.6 (5.1)	− 0.7 (3.6)	1.89	.063
Core Disruptiveness[g]	91	3.0 (2.7)	− 0.7 (2.2)	3.03	.003
Aberrant Motor	91	3.4 (3.8)	− 0.7 (3.5)	1.88	.064
Agitation/Aggression	91	4.3 (3.5)	− 1.2 (3.5)	3.28	.001
Anxiety	91	2.9 (3.6)	− 0.8 (3.5)	2.05	.043
Apathy/Indifference	91	2.1 (3.8)	0.0 (3.2)	0.03	.974
Appetite/Eating Chg.	90	1.4 (3.0)	− 0.1 (3.2)	0.17	.868
Delusions	91	2.4 (3.1)	− 0.6 (2.4)	2.30	.024
Depression/Dysph.	91	1.6 (3.3)	− 0.3 (2.9)	1.02	.312
Disinhibition	91	2.4 (3.8)	− 0.7 (2.3)	2.78	.007
Euphoria/Elation	91	0.4 (1.7)	− 0.1 (0.8)	0.80	.426
Hallucinations	91	1.2 (2.7)	− 0.1 (1.7)	0.80	.428
Irritability/Lability	91	4.0 (3.6)	− 1.2 (3.5)	3.16	.002
Night-Time Behavior	91	1.8 (3.4)	− 0.6 (3.2)	1.89	.062
BPRS Total	76	24.4 (11.7)	− 2.5 (8.3)	2.67	.009
Negative cluster	91	4.3 (3.9)	0.2 (3.1)	0.65	.515
Positive cluster	77	6.8 (4.0)	− 0.6 (3.4)	1.66	.101
Anxiety/Depression	79	3.6 (3.1)	− 0.6 (2.5)	2.11	.038
CGI-S Alzheimer's	105	4.6 (0.9)	0.1 (0.6)	2.24	.027
Psychosis	105	3.4 (1.2)	− 0.2 (1.2)	1.74	.085
MMSE Total	89	7.0 (6.9)	− 0.7 (3.8)	1.62	.108

[a]Numbers < 105 reflect missing endpoint scores for some patients.
[b]Baseline was defined from the last non-olanzapine visit prior to the open-label phase.
[c]Mean change from baseline to endpoint, last observation carried forward.
[d]p values for change were calculated by Student's t test (two-sided).
[e]Sum of NPI/NH *Agitation/Aggression*, *Hallucinations*, and *Delusions* item scores.
[f]Sum of NPI/NH *Hallucinations* and *Delusions* item scores.
[g]Occupational disruptiveness of caregivers for the NPI/NH items of *Agitation/Aggression*, *Hallucinations*, and *Delusions*.
BPRS, Brief Psychiatric Rating Scale; CGI-S Alzheimer's, Clinical Global Impressions Severity of Alzheimer's Dementia; CGI-S Psychosis, Clinical Global Impressions Severity of Psychosis; *Dysph.*, NPI/NH *Dysphoria* item; MMSE, Mini-Mental State Exam; NPI/NH, Neuropsychiatric Inventory—Nursing Home version; SD, standard deviation.

scores were not significantly changed from baseline. In general, subgroup analysis revealed no significant differences in any efficacy score based on age (< 85 *vs* ≥ 85), sex, or ethnic origin.

Safety results

Olanzapine treatment was well tolerated, as patients experienced little or no extrapyramidal symptoms. At endpoint, Simpson–Angus total scores were not significantly changed from baseline (mean change, 0.6 ± 3.0; $t = 1.84$, $n = 85$, $p = .069$), indicating little or no increase in the incidence of parkinsonian symptoms. AIMS scores, indicative of dystonias and dyskinesias, were also unchanged from baseline (0.0 ± 1.8; $t = 0.16$, $n = 104$, $p = .871$). Levels of akathisia, as measured by Barnes Global scores, continued to improve significantly under olanzapine treatment (− 0.2 ± 0.6, $t = 2.40$, $n = 102$, $p = .018$) from a baseline at the end of the acute phase of 0.2 (SD = 0.6).

Treatment-emergent adverse events occurring with an incidence greater than 10% are shown in Table 3. Somnolence had the greatest incidence (27.6%). As a treatment-emergent event, weight gain was reported by 9.5% of patients, whereas weight loss was reported by 16.2%. Three patients had adverse events of both weight gain and weight loss. The overall mean change in weight for the entire treatment group was not significantly changed (− 0.2 ± 3.6 kg, $t = 0.51$, $n = 104$, $p = .608$). Patients showing treatment-emergent weight gain but not weight loss ($n = 7$) showed a mean increase of 4.3 kg (SD = 4.0), while those showing treatment-emergent weight loss but not weight gain ($n = 14$) experienced a 4.4-kg decrease (SD = 4.0). Weight loss among the ten patients receiving a 15-mg/d modal dose was not associated with somnolence. No significant changes were seen in any other vital sign or cardiovascular parameter, including orthostasis and corrected QT interval (− 0.94 ± 26.1 ms, $t = 0.34$, $n = 89$, $p = .736$). One patient, who showed evidence of borderline hypergly-

Table 3. Treatment-emergent adverse events (total patients, $n = 105$)[a]

COSTART Term[b]	n (%)
Somnolence	29 (27.6)
Accidental Injury[c]	26 (24.8)
Rash[d]	19 (18.1)
Increased Cough	18 (17.1)
Weight Loss	17 (16.2)
Rhinitis	16 (15.2)
Fever	15 (14.3)
Abnormal Gait[e]	14 (13.3)
Constipation	14 (13.3)
Ecchymosis	14 (13.3)
Diarrhoea	12 (11.4)
Urinary Tract Infection	12 (11.4)
Infection	11 (10.5)

[a]Events occurring with a frequency of 10% or greater, occurring or worsening after baseline, regardless of cause.
[b]Coding Symbols for a Thesaurus of Adverse Reaction Terms.
[c]Term comprises abrasion, bruise, fall, fracture, laceration, and skin tear.
[d]Term comprises dermatitis, erythema, rash, reddened skin, and skin irritation.
[e]Term comprises leaning, limp, stooped posture, and unsteady gait.

cemia at baseline, met the criteria for hyperglycemia (160 mg/dL, or 8.816 SI units) at endpoint. Two other patients who were euglycemic at baseline were mildly hyperglycemic by endpoint (162–167 mg/dL, or 8.993–9.270 SI units). One of these had shown evidence of borderline hyperglycemia at baseline for the acute phase. Finally, in contrast, two patients who met the criteria of the American Diabetic Association for diabetes (200 mg/dL, or 11.102 SI units) at baseline were euglycemic by endpoint. No other clinically significant or potentially clinically significant changes were seen among patients in any other laboratory analyte.

DISCUSSION

The results of this study indicate that, when used for an additional 18 weeks beyond an initial 6-week period, olanzapine continues to increase its control over behavioral disturbances and psychotic symptoms in elderly patients with AD. As indicated by the primary measure of efficacy, comprising the sum of the individual scores of the NPI/NH *Agitation/Aggression*, *Hallucinations*, and *Delusions* items (Core Total), patients' symptoms on average were reduced further over the additional 18-week period by approximately one-fourth. Significant reductions were seen in five of the ten individual behavioral items of the NPI/NH, as well as in the Occupational Disruptiveness scores associated with the symptoms of the Core Total, the

BPRS total, and CGI Severity of Dementia scores. Simultaneously, MMSE scores showed no significant change from baseline, indicating that patients' cognitive states were stable. Further clinical response to treatment during the extension phase, defined as a $\geq 50\%$ reduction in Core Total score from the end of the acute phase, was obtained in approximately half of all olanzapine-treated patients.

Long-term studies of the efficacy of atypical antipsychotics in elderly patients have been limited in number. To our knowledge, the only other structured study lasting over four months in duration and investigating the use of antipsychotics in elderly patients with dementia has been a single open-label study of risperidone use in nursing home patients with a variety of classes of dementia (Goldberg and Goldberg, 1997). This study found risperidone to be 'helpful' in 38% of the patients studied and 'moderately helpful' in another 26%. The present study is therefore the first to use objective measures of the efficacy and safety of an antipsychotic in AD patients over a period longer than four months. Using a shorter, 12-week duration as the criterion, most long-term studies that have been conducted to date have likewise involved risperidone (De Deyn *et al.*, 1999; Katz *et al.*, 1999; Madhusoodanan *et al.*, 1999). Both De Deyn *et al.* (1999) and Katz *et al.* (1999) conducted large double-blind, placebo-controlled studies in which institutionalized patients with AD, vascular dementia, or mixed dementia received up to 4 mg/day of risperidone for 12 or 13 weeks. In both studies, patients showed significant improvements from baseline on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Katz *et al.* (1999) also found significant improvements in patients' Cohen–Mansfield Agitation Inventory and CGI scores. However, the percentage of patients who met the primary objective in the De Deyn *et al.* study ($\geq 30\%$ reduction in BEHAVE-AD scores) was not significantly greater than placebo (De Deyn *et al.*, 1999). A 12-week interim analysis from a year-long open-label study involving quetiapine (McManus *et al.*, 1999) has demonstrated that this atypical antipsychotic may also show promise in controlling psychotic symptoms in elderly patients with various forms of psychosis, while a retrospective chart review of clozapine use (Salzman *et al.*, 1995) indicates that this agent, structurally related to olanzapine, brings about 'modest' improvement in psychotic symptoms in elderly patients with psychosis and behavioral disturbances.

Long-term studies in elderly demented patients with the classical antipsychotics have been notably

lacking. For the most part, studies with these agents have been limited to eight weeks or less. The findings for haloperidol have been mixed. In two crossover studies (Sugarman *et al.*, 1964; Devanand *et al.*, 1998), 2 to 4.5 mg/d of haloperidol was slightly but significantly more effective than placebo in controlling psychosis and psychomotor agitation, with response rates of 55% to 60% (Devanand *et al.*, 1998). However, another study (Auchus and Bissey-Black, 1997) found that 3 mg/d of haloperidol was no more effective than placebo in reducing agitation, but was associated with much greater toxicity. Likewise, one study has reported a slight improvement with chlorpromazine (Birkett and Boltuch, 1972), but several studies indicate a rate of deterioration that is similar to or higher than that seen among patients receiving placebo (Robinson, 1959; Birkett and Boltuch, 1972) Results with thioridazine have also been inconsistent. A six-week study (Phanjoo and Link, 1990) involving nine patients taking 50–200 mg demonstrated a significant reduction of patients' BPRS total scores from 24 to 7, although only one patient was rated as 'very much improved' on the CGI-S. By contrast, an eight-week study (Barnes *et al.*, 1982) found that thioridazine was no better than placebo on any item of the BPRS or on the Sandoz Clinical Assessment–Geriatric scale, but this may have been due to the use of a 25-mg/d dose, which may have been inadequate. Caution is suggested with the use of thioridazine, which has been said by some to have only an anxiolytic effect to support its use, while excessive side effects may warrant its reconsideration (Kirchner *et al.*, 2000). More recent results with thiothixene (Finkel *et al.*, 1995) have been encouraging, as have the findings with zuclopenthixol, of which both oral administration (Nygaard *et al.*, 1994) and intramuscular depot injection (Robles *et al.*, 1996) have demonstrated significant efficacy of this agent, with minimal extrapyramidal toxicity.

In the present study, two-thirds of the patients entering the open-label phase completed the 18-week trial. Of the 35 olanzapine-treated patients who discontinued, 21 (20%) did so due to adverse events, and none due to lack of efficacy. By contrast, adverse event rates as high as 83% have been noted with risperidone (De Deyn *et al.*, 1999; Madhusoodanan *et al.*, 1999), with as much as 44% of discontinuations being due to lack of efficacy (De Deyn *et al.*, 1999). The most commonly reported adverse events associated with olanzapine use here were somnolence and accidental injury. As might be expected from agents that block central histaminergic and noradre-nergic receptors (Tamminga *et al.*, 1987), somnolence rates above 10% are commonly reported during treatment with atypical antipsychotics (Katz *et al.*, 1999; McManus *et al.*, 1999).

As identified by objective measures, no evidence of extrapyramidal symptoms (EPS) were seen in this study. In fact, measures of akathisia, which had showed significant improvement from baseline during the acute phase (Street *et al.*, 2000), continued to improve during the extension phase. This putatively is one of the strengths of the atypical antipsychotics over the classical antipsychotics, some of which are associated with EPS incidence rates on the order of 60% (Devanand *et al.*, 1998), although EPS liability rates have also been noted to be as high as 50% to 53% in some open-label studies involving risperidone (Herrmann *et al.*, 1998; Lavretsky and Sultzer, 1998). EPS risk is a particular concern in elderly patients, particularly those with AD, who are at greater risk of neuroleptic-induced parkinsonism (Caligiuri *et al.*, 1998; Caligiuri *et al.*, 1999).

No significant changes were seen in vital signs, and no evidence of orthostatic hypotension was seen in the present study. Electrocardiographic parameters were not significantly changed. This contrasts with the QT interval prolongation often seen with classical antipsychotics (Lawrence and Nasraway, 1997; Drici *et al.*, 1998; Reilly *et al.*, 2000; Welch and Chue, 2000). This dangerous condition is also associated with use of ziprasidone (Gury *et al.*, 2000; Pfizer Pharmaceuticals, 2000). Laboratory analytes were essentially unchanged. Weight gain has been a particular concern with olanzapine. However, weight gain as a treatment-emergent event was seen in the present study in fewer than 10% of patients, while weight loss was seen in 16%. Overall, mean weight changes from baseline were not significant. Analysis showed that weight increases were not related to changes in non-fasting glucose levels.

Among the treatment-emergent events that were observed during this study, 'rash' occurred in 18.1% of patients, and 'accidental injury' occurred in 13.3%. These terms are those which appear in the Coding Symbol and Thesaurus for Adverse Reaction Terms (COSTART), and encompass a variety of actual terms. 'Rash' includes such dermatological conditions as reddened skin, erythema, and other forms of skin irritation, as well as dermatitis and actual rash. 'Accidental injury' was broadly defined to include abrasions, bruises, lacerations, and skin tears, as well as fractures and falls. In view of the fragility of this elderly population, the 13% to 18% incidences rates seen here are not surprising, and are in line with those

seen in untreated elderly populations (Street *et al.*, 2000).

As with any open-label study, the present study was not without its limitations. The absence of a comparator and the unrestricted use of benzodiazepine, although minimal, both make it difficult to assess the full effect of olanzapine in isolation. Moreover, the study used a flexible-dosing schedule, with mean efficacy data being derived from all patients regardless of the doses they actually received. It was therefore not possible to obtain any indication of dose effects. These points notwithstanding, however, the intent of this study was to observe long-term safety and efficacy of olanzapine in a well-defined population of patients without concern for dose responses, the effects of dose-switching, or times to event.

In summary, this study showed that, following an initial 6-week exposure to olanzapine, an additional 4–5 months of treatment was associated with a significant further improvement in delusory symptoms and in levels of agitation, aggression, anxiety, and depression in nursing home patients with AD. Cognition was not significantly changed from baseline, and overall mean weight change, vital signs, electrocardiography, and laboratory analytes overall were not substantially altered. The most common adverse event was somnolence. Accordingly olanzapine, particularly the modal dose of 5 mg/d, appears to be an effective and generally well-tolerated treatment for behavioral disturbances and psychotic symptoms due to Alzheimer's dementia in elderly patients.

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