A Review of Treatment-Emergent Adverse Events During Olanzapine Clinical Trials in Elderly Patients With Dementia

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Objective: Olanzapine and other antipsychotics are not approved by the U.S. Food and Drug Administration to treat behavioral disturbances associated with dementia, but they are often prescribed to these patients. Although antipsychotics may be efficacious in this population, elderly patients with dementia may be particularly vulnerable to adverse events. This article reviews the safety of olanzapine in elderly patients with dementia.

Data Sources: Data from 6 studies comparing olanzapine to placebo, risperidone, or conventional antipsychotics in elderly patients with dementia were analyzed for mortality, cerebrovascular adverse events (CVAEs), and other adverse events. These trials represent all Lilly olanzapine-comparator trials in this population. The data included integration of 5 double-blind, placebo-controlled studies (olanzapine, N = 1184; placebo, N = 478; median age = 79 years; 1 study also compared olanzapine with risperidone, N = 196) and an open-label study comparing olanzapine (N = 150) with conventional antipsychotics (N = 143).

Data Synthesis: Incidence of mortality was significantly higher in olanzapine- (3.5%) than in placebo-treated patients (1.5%; p = .024). There were no significant differences in the crude incidence of mortality between olanzapine- (2.9%) and risperidone- (2.0%) or olanzapine- (14.8%) and conventional antipsychotic–treated patients (16.1%; p = .871). Risk factors associated with mortality in olanzapine-treated patients included age ≥ 80, concurrent benzodiazepine use, treatment-emergent sedation, or treatment-emergent pulmonary conditions. Incidence of CVAEs was approximately 3 times higher in olanzapine- (1.3%) than in placebo-treated patients (0.4%). There were no significant differences in the incidence of CVAEs between olanzapine- (2.5%) and risperidone- (2.0%; p = 1.0) or olanzapine- (3.4%) and conventional antipsychotic–treated patients (4.3%; p = .765).

Conclusion: These findings should be considered if prescribers elect to treat behavioral disturbances associated with dementia in the elderly with olanzapine or other antipsychotics.

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Antipsychotic agents are not approved by the U.S. Food and Drug Administration (FDA) for the treatment of behavioral disturbances associated with dementia. In fact, after reviewing 17 placebo-controlled studies of the atypical antipsychotics aripiprazole, quetiapine, risperidone, and olanzapine (including the 5 studies presented in this analysis), the FDA concluded that the mortality rate in elderly patients with dementia treated with atypical antipsychotics was 1.6 to 1.7 times that in those treated with placebo; therefore, all U.S. manufacturing product inserts for atypical antipsychotics now contain a "black box" warning.[1] Nevertheless, antipsychotics are often prescribed off label to these patients. Last year, antipsychotic use in patients with dementia represented almost half of all antipsychotic use in patients over the age of 65 years.[2] This perhaps reflects a significant clinical need and a paucity of available, effective treatments. However, treating this population safely and effectively can be challenging because comorbid illness[3] and polypharmacy[4] become more frequent with aging. Moreover, natural age-related alterations in pharmacokinetics and pharmacodynamics, including changes in drug response and the ability to metabolize drugs,[5] may potentially cause the elderly to be more susceptible to treatment-emergent adverse events.[5–7]

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Treating elderly patients becomes more difficult when there is a diagnosis of dementia.[8] Patients with dementia have mortality rates twice those of the elderly population without dementia, and the risk of mortality increases with the duration of dementia. The risk is further increased when a comorbid medical condition is present. These patients may also be at a greater risk for experiencing cerebrovascular adverse events (CVAEs). In patients with a history of CVAEs, those with dementia tend to have more severe cerebrovascular disease and more CVAE risk factors than those without dementia.[9] Because of the vulnerability of elderly patients with dementia, clinicians considering antipsychotic treatment should carefully weigh the potential risks for patients in this population who may be treated with these drugs. Knowledge of the factors that may potentially increase an individual's risk for treatment-emergent adverse events may be useful to prescribers in making these treatment decisions. While several literature reviews and analyses on the use of antipsychotics in elderly patients with dementia are available,[4,10,11] this is the first integrated analysis focusing on adverse events in this population. Data from 6 clinical trials in elderly patients with behavioral disturbances associated with dementia treated with olanzapine, risperidone, conventional antipsychotics, or placebo are presented. These represent all Lilly olanzapine-comparator trials in this population.

METHOD

Study Selection and Design

Data from 6 studies comparing olanzapine with placebo, risperidone, or conventional antipsychotics conducted by Eli Lilly and Company (studies HGAO, HGEU, HGGU, HGIC, HGIV, and HGGE; conducted from 1994–2002) were analyzed to assess the safety of olanzapine in elderly patients with Alzheimer's disease, vascular dementia, mixed dementia, or dementia not otherwise specified. These trials represent all the Lilly olanzapine double-blind, placebo-controlled trials in this population as well as an open-label study of olanzapine and conventional antipsychotics.

Study HGAO was a double-blind, placebo-controlled study evaluating olanzapine safety in patients with primary degenerative dementia of the Alzheimer's type, with psychotic symptoms and behavioral disturbances. Studies HGEU and HGIV were double-blind, placebo-controlled trials investigating olanzapine treatment in psychosis and/or behavioral disorders associated with Alzheimer's disease. Study HGGU (also with a risperidone comparison, N = 196) was a double-blind, placebo-controlled trial investigating olanzapine treatment in psychosis and/or behavioral disorders associated with various forms of dementia (most patients in study HGGU had a diagnosis of Alzheimer's disease, but a small number had a diagnosis of mixed or vascular dementia). Study HGIC was a double-blind, placebo-controlled study investigating olanzapine treatment of mild to moderate cognitive deficits associated with Alzheimer's disease in patients without psychosis and agitation. Study HGGE was an open-label safety study comparing olanzapine (N =150) and conventional antipsychotic (N = 143) use in the development of tardive dyskinesia in elderly patients with various psychiatric illnesses (although most had dementia-related psychosis). From these 6 trials, the 5 double-blind, placebo-controlled studies (HGAO, HGEU, HGGU, HGIC, and HGIV) were combined to create the integrated database (olanzapine, N = 1184; placebo, N = 478; median age = 79 years). The duration of each trial and dosing schedules are presented in Table 1.

The incidence of mortality and CVAEs in olanzapine-, risperidone-, conventional antipsychotic–, and placebo-treated patients were analyzed from all 6 studies. Abnormal laboratory values, vital signs, and other adverse events were analyzed from the integrated database; adverse events and other data from studies HGGE[12] and HGGU[13] have been previously reported. Primary data and other results from these studies also have been previously reported for studies HGEU,[14–20] HGGU,[13] HGGE,[12] HGIC,[21] and HGIV.[22,23] The primary data have not been published from study HGAO. The results of these clinical trials are or will be available on the Lilly Clinical Trial Registry (http://www.lillytrials.com) and the National Institutes of Health clinical trial registry (http://clinicaltrials.gov).

Outcome Variables and Definition of Outcome Variables

Incidence of mortality included patient deaths occurring during and 30 days immediately following the last dose of the study drug. Potential risk factors for mortality were identified by a physician as those variables that may be clinically relevant and were evaluated in the integrated database. These included baseline factors of age, sex, Mini-Mental State Examination (MMSE) score, sedation, malnutrition/dehydration, extrapyramidal symptoms, body mass index, and pulmonary conditions, as well as the treatment-emergent factors of number of concomitant medications, change in weight (≥ 7% of baseline), sedation, malnutrition/dehydration, extrapyramidal symptoms, dysphagia, pulmonary conditions, and benzodiazepine use.

The potential relationship between dose of olanzapine and mortality was also examined. Organ systems potentially involved at the terminal event were identified from case narratives, as not all information was available on the cause of death in each mortality case. Two physicians independently investigated the medical conditions present at baseline and terminal event in olanzapine- and placebo-treated patients in the integrated database. Organ

Table 1. A Summary of the 6 Lilly Olanzapine Comparator Trials in Elderly Patients With Behavioral Disturbances Associated With Dementia[a]

Study	Patient Population	N	Study Duration, wk	Mean (SD) Age, y	Dosing Schedule and Dosages, mg/day[b]	Primary Efficacy Measure and Mean (SD) Change in Score[c]	p Value[d]
HGAO	Alzheimer-related psychosis[e]	OLZ: 120 PLC: 118	Acute: 8 Extension[f]: 14	OLZ: 78.2 (6.9) PLC: 78.9 (6.3)	Flexible Acute: 1–8 Extension: 1–8	BEHAVE-AD OLZ: –3.72 (8.2) PLC: –3.32 (8.9)	.39
HGEU	Alzheimer-related psychosis/behavioral disturbances[g]	OLZ, 5.0: 56 OLZ, 10.0: 50 OLZ, 15.0: 54 PLC: 47	Acute: 6 Extension[f]: 18	OLZ, 5.0: 82.9 (6.5) OLZ, 10.0: 83.6 (6.5) OLZ, 15.0: 83.1 (6.6) PLC: 81.4 (6.8)	Fixed 5.0, 10.0, 15.0	NPI/NH Core Total OLZ, 5.0: –7.6 (7.7) OLZ, 10.0: –6.1 (8.2) OLZ, 15.0: –5.2 (8.0) PLC: –3.3 (10.0)	< .001 .01 .23
HGGU	Dementia-related psychosis/behavioral disturbances[g,h]	OLZ: 204 RISP: 196 PLC: 94	Acute: 10 Extension[i]: 16	OLZ: 77.9 (7.7) RISP: 78.0 (6.9) PLC: 79.8 (7.2)	Flexible OLZ: 2.5–10.0 RISP: 0.5–2.0	NPI/NH Psychosis Total OLZ: –4.0 (6.3) RISP: –4.3 (6.0) PLC: –5.2 (5.4)	.49 .28
HGIC	Cognitive symptoms in Alzheimer's, without psychosis and agitation[g]	OLZ: 178 PLC: 90	Acute: 12 Extension[j]: 14	OLZ: 77.6 (8.0) PLC: 77.7 (7.8)	Fixed 2.5, 5.0	ADAS-Cog OLZ: 4.1 (0.6) PLC: 1.4 (0.8)	< .01
HGIV	Alzheimer's-related psychosis/behavioral disturbances[g]	OLZ, 1.0: 129 OLZ, 2.5: 135 OLZ, 5.0: 127 OLZ, 7.5: 132 PLC: 129	Acute: 10 Extension[j]: 16	OLZ, 1.0: 76.4 (11.6) OLZ, 2.5: 76.9 (10.2) OLZ, 5.0: 76.6 (9.2) OLZ, 7.5: 76.5 (10.1) PLC: 76.7 (10.7)	Fixed 1.0, 2.5, 5.0, or 7.5	NPI/NH (mean [SE]) OLZ, 1.0: –1.6 (0.3) OLZ, 2.5: –2.0 (0.3) OLZ, 5.0: –2.2 (0.3) OLZ, 7.5: –1.9 (0.3) PLC: –1.2 (0.3)	.31 .03 .01 .07
HGGE[k]	Tardive dyskinesia[l]	OLZ: 150 CONV: 143	Open label: 59	OLZ: 78.0 (8.3) CONV: 78.9 (8.1)	Flexible OLZ: 2.5–20.0 CONV: per manufacturer recommendations	CGI-S OLZ: –21.5 (20.7) CONV: –15.5 (21.1)	

[a]The primary objectives for these studies were safety measures. Methods have been previously described in studies HGEU,[14–20] HGGU,[13] HGGE,[12,18] HGIC,[21] and HGIV.[22,23] Data from study HGAO were analyzed using a Type III sum of squares.
[b]All study doses refer to olanzapine doses, unless otherwise specified.
[c]Efficacy outcomes are mean changes in the primary efficacy measure for each study in the acute phase of the trial.
[d]p Values are derived from the olanzapine versus placebo comparison, except in studies HGGU and HGGE.
[e]DSM-III-R.
[f]Open-label extension phase.
[g]National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.
[h]DSM-IV.
[i]Open-label, extension phase for responders.
[j]Double-blind extension phase.
[k]All trials were double-blind placebo-controlled trials with the exception of study HGGE, which was an open-label comparison between olanzapine and conventional antipsychotics (no p values shown, as data have not yet been analyzed).
[l]DSM-IV-TR.
Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognition, BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease rating scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CONV = conventional antipsychotics, NPI/NH = Neuropsychiatric Inventory-Nursing Home, OLZ = olanzapine, PLC = placebo, RISP = risperidone.

systems involved at terminal event were defined as those multiple clinical conditions that may have possibly contributed to a patient's death. These categories were not mutually exclusive, as a single patient could have involvement of more than 1 organ system. The physicians independently reviewed the case narratives of the patients who died and later reached a consensus on the organ systems affected at baseline and terminal event. CVAEs were defined as hemorrhagic strokes, ischemic strokes, cerebrovascular accidents, or transient ischemic attacks. Potential risk factors for CVAEs were identified in a letter from the FDA (dated 7/2/02), and included age, sex, baseline MMSE score, treatment-emergent orthostatic hypotension, and dementia diagnosis, and were examined in the integrated database, study HGGE, and the olanzapine and risperidone arms of study HGGU.

Baseline sedation, malnutrition/dehydration, extrapyramidal symptoms, body mass index, and pulmonary conditions and treatment-emergent sedation, pulmonary conditions, number of concomitant medications, change in weight, malnutrition/dehydration, extrapyramidal symptoms, and dysphagia were examined as potential risk factors for mortality, but not for CVAEs. Orthostatic hypotension was examined as a potential risk factor for CVAEs, but not mortality. No vital signs or laboratory values were analyzed as potential risk factors for mortality or CVAEs.

All other treatment-emergent adverse events analyzed from the integrated database were defined as events that first occurred or worsened after baseline. A treatment-emergent abnormal laboratory value was defined as a change from normal at baseline to abnormal at any time during treatment. A high laboratory value was defined as a change from a value less than or equal to the upper bound of the reference range at baseline to a value greater than the upper bound of the reference range at any time during treatment. A low laboratory value was defined as a change from a value greater than or equal to the lower bound of the reference range at baseline to a value less than the lower bound of the reference range at any time during treatment. Lilly reference ranges were used to determine the high and low limits for each laboratory analyte, and were adjusted for age, ethnicity, and sex. Vital sign information, including weight, heart rate, and systolic blood pressure, was evaluated. Abnormal weight change was defined as weight change of ≥ 7% from baseline body weight. Treatment-emergent low supine systolic blood pressure was defined as ≤ 90 mm Hg and a decrease ≥ 20 mm Hg; treatment-emergent high supine systolic blood pressure was defined as ≥ 180 mm Hg and an increase ≥ 20 mm Hg.

Statistical Analysis

Fisher exact test was used to compare the crude incidences of mortality, the relationship between dose and the incidence of mortality, CVAEs, adverse events, and treatment-emergent changes in vital signs and laboratory values from the integrated database. A meta-analysis was also conducted comparing the percentages of mortality and CVAEs between the 2 treatment groups. The meta-analysis models for the exposure-adjusted incidence rate differences (IRD = olanzapine – placebo) for mortality and CVAEs were based on the method described by Greenland and Robins.[24] This method averages the individual study incidence differences, including studies with no events (i.e., IRD = 0), while weighting by the number of subjects in each study and assuming a fixed effect of therapy across studies. Risk factors for mortality were identified as those characteristics with a significant association with mortality using Fisher exact test; risk factors for CVAEs were identified as those characteristics with a significant association with CVAEs using logistic regression. Mean changes from baseline to endpoint in vital signs and laboratory values were assessed using an analysis of variance model, which included the variables treatment and protocol.

RESULTS

Patient Characteristics

The integrated database contained 1184 olanzapine- and 478 placebo-treated patients. Study HGGU contained 204 olanzapine-, 94 placebo- (both included in the integrated database), and 196 risperidone-treated patients; study HGGE contained 150 olanzapine- and 143 conventional antipsychotic–treated patients. Patients did not significantly differ between treatment groups in age, sex, or ethnicity ($p > .05$). The majority of the patients were female and white. Alzheimer's disease was the most common diagnosis; however, in study HGGE, 35 olanzapine- and 25 conventional antipsychotic–treated patients had a diagnosis other than dementia, including schizophrenia, schizoaffective disorder, delusional disorder, psychotic delusional disorder, major depressive disorder, and bipolar I disorder.

Significantly more olanzapine-treated patients discontinued the placebo-controlled trials because of an adverse event than did patients treated with placebo (13.3%, N = 157/1184 vs. 6.7%, N = 32/478, respectively; $p < .001$) or risperidone (16.2%, N = 33/204 vs. 8.7%, N = 17/196, respectively; $p = .02$). There were no significant differences in the discontinuation rates between olanzapine- and conventional antipsychotic–treated patients (17.3%, N = 26/150 vs. 20.3%, N = 29/143, respectively; $p = .55$). In the integrated database, agitation was the most common reason for discontinuation for both olanzapine- (0.7%, N = 8/1184) and placebo-treated patients (0.6%, N = 3/478, $p = 1.0$). There were no statistically significant discontinuations due to any single category of adverse events.

Table 2. Crude Incidence Rates of Mortality and Cerebrovascular Adverse Events (CVAEs) in Elderly Patients With Dementia From the Integrated Database, Study HGGU, and Study HGGE

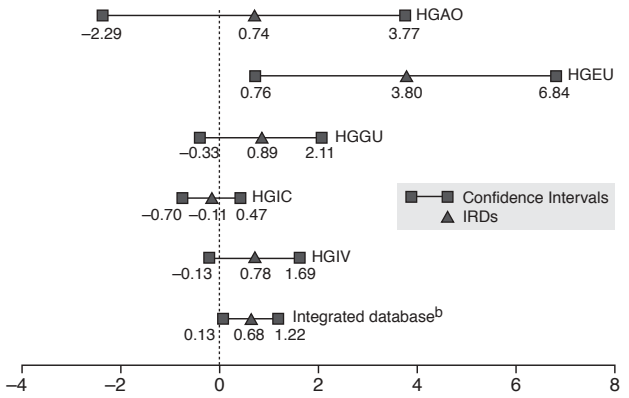
	Mortality			CVAEs		
Study	N/N	%	p Value[a]	N/N	%	p Value[a]
HGAO						
Olanzapine	3/120	2.5	1.00	0/118[b]	0.0	1.00
Placebo	2/118	1.7		1/118	0.8	
HGEU						
Olanzapine	6/159	3.8	.34	1/159	0.6	1.00
Placebo	0/47	0.0		0/47	0.0	
HGGU						
Olanzapine	6/204	2.9	.44	5/204	2.5	.33
Placebo	1/94	1.1		0/94	0.0	
HGIC						
Olanzapine	1/178	0.6	1.00	5/177[b]	2.8	.67
Placebo	1/90	1.1		1/90	1.1	
HGIV						
Olanzapine	26/523	5.0	.24	4/520[b]	0.8	1.00
Placebo	3/129	2.3		0/129	0.0	
Integrated Total						
Olanzapine	42/1184	3.5	.02	15/1178[c]	1.3	.18
Placebo	7/478	1.5		2/478	0.4	
HGGU						
Olanzapine	6/204	2.9	.75	5/204	2.5	1.00
Risperidone	4/196	2.0		4/196	2.0	
HGGE						
Olanzapine[d]	22/149	14.8	.87	5/149	3.4	.77
Conventional antipsychotics	23/143	16.1		6/141[b]	4.3	

[a]Fisher exact test.
[b]The number of patients in CVAE analysis excludes a total of 8 patients (6 from the integrated database [studies HGAO, HGIC, and HGIV] and 2 from study HGGE) who were randomly assigned to, but did not receive, treatment. The mortality analysis was predefined as an intent-to-treat analysis and included all patients randomly assigned to treatment.
[c]Excludes 6 patients who were randomly assigned to, but did not receive, treatment.
[d]Excludes 1 patient who was randomly assigned to, but did not receive, treatment.

Mortality

The crude incidence of mortality in the integrated database was significantly higher (more than twice as high) in olanzapine- (3.5%, N = 42/1184) compared with placebo-treated patients (1.5%, N = 7/478; p = .024, Fisher exact test). Similarly, a meta-analysis, stratified by protocol, showed a significant non–exposure-adjusted incidence rate difference (IRD = 0.017, p = .029) and exposure-adjusted incidence rate difference in mortality (IRD = 0.677, p = .015), with a higher incidence in olanzapine- than in placebo-treated patients. In the active comparator trials, there were no significant differences in the crude incidence of mortality between olanzapine- (2.9%, N = 6/204) and risperidone-treated patients (2.0%, N = 4/196; p = .751; HGGU), or olanzapine- (14.8%, N = 22/149) and conventional antipsychotic–treated patients (16.1%, N = 23/143; p = .871; HGGE). There were no significant differences in the exposure-adjusted incidence rates of mortality between olanzapine- and risperidone-, or olanzapine- and conventional antipsychotic–treated patients. Crude incidence rates for mortality from all 6 studies are presented by individual study in Table 2, and the individual exposure-adjusted incidence rate differences from the double-blind, placebo-controlled studies are presented in Figure 1. There was no significant relationship between highest dose of olanzapine and incidence of mortality (Table 3).

Figure 1. Meta-Analysis, Stratified by Protocol, of Exposure-Adjusted Incidence Rate Differences (IRDs) of Mortality in Olanzapine-Treated Patients From the 5 Double-Blind Placebo-Controlled Clinical Trials and the Integrated Database[a]



[a]IRD values greater than zero indicate a higher incidence and those less than zero indicate a lower incidence of mortality in the olanzapine- than in placebo-treated patients. Confidence intervals not overlapping zero indicate a significant IRD between 2 treatment groups. Values for the integrated comparison used the fixed effects meta-analysis.
[b]p = .015.

Table 3. The Relationship Between Dose of Olanzapine and the Incidence of Mortality in Elderly Patients With Dementia Treated With Olanzapine in the Integrated Database, Study HGGU, and Study HGGE[a]

	Mortality		
Highest Dose, mg	N/N	%	p Value
Integrated Database[b]			.557
1.0 to ≤ 5.0	26/801	3.2	
> 5.0 to ≤ 7.5	10/197	5.1	
> 7.5 to ≤ 10.0	5/116	4.3	
> 10.0 to ≤ 15.0	1/61	1.6	
> 15.0 to ≤ 20.0	0/2	0.0	
HGGU[c]			.763
1.0 to ≤ 5.0	4/96	4.2	
> 5.0 to ≤ 7.5	1/50	2.0	
> 7.5 to ≤ 10.0	1/57	1.8	
HGGE[d]			.486
1.0 to ≤ 10.0	17/120	14.2	
> 10.0 to ≤ 20.0	5/21	23.8	
> 20.0 to ≤ 30.0	0/4	0.0	
> 30.0 to ≤ 40.0	0/1	0.0	

[a]Frequencies were analyzed using Fisher exact test.
[b]Excludes 6 patients who were randomly assigned to olanzapine but did not receive treatment and 1 patient for whom information was not available.
[c]Data not available for 1 patient.
[d]Data not available for 3 patients.

Table 4. Risk Factors Associated With Mortality in All Elderly Patients With Dementia-Related Psychosis Treated With Olanzapine or Placebo From the Integrated Database

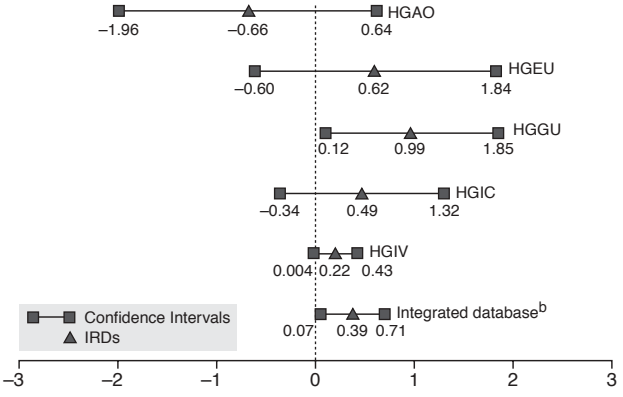
Risk Factor	Mortality			Overall p Value[a]	Other p Value[a]
	Yes	No	%		
Age, y[b]					
< 65	1	127	0.8	.02	
65 to < 80	16	751	2.1		
≥ 80	32	735	4.2		< .01 (< 80 vs ≥ 80)
MMSE score[b]					
Mild impairment (19–30)	4	449	0.9	< .001	< .01 (mild + moderate vs severe)
Moderate impairment (10–18)	21	702	2.9		< .01 (mild vs moderate + severe)
Severe impairment (≤ 9)	24	455	5.0		
Benzodiazapine use					
Yes	30	699	4.1	.02	
No	19	914	2.0		
Sedation[c]					
Yes	16	120	11.8	< .001	
No	33	1493	2.2		
Pulmonary conditions[c]					
Yes	26	182	12.5	< .001	
No	23	1431	1.6		
Change in weight[c]					
Loss ≥ 7%	6	69	8.0	.02	.02 (loss vs no change + gain)
No change	36	1324	2.6		
Gain ≥ 7%	2	169	1.2		
Malnutrition/dehydration[c]					
Yes	13	239	5.2	.04	
No	36	1374	2.6		
Dysphagia[c]					
Yes	4	15	21.1	< .01	
No	45	1598	2.7		

[a]Fisher exact test.
[b]Baseline; not all patients had a baseline MMSE score.
[c]Treatment emergent; not available for all patients.
Abbreviation: MMSE = Mini-Mental State Examination.

Risk factors for mortality. Statistically significant risk factors for mortality in both olanzapine- and placebo-treated patients in the integrated database are presented in Table 4. These included baseline age ≥ 80 years, low baseline MMSE score (defined as a score of ≤ 18), concurrent benzodiazepine use, and the following treatment-emergent adverse events: pulmonary conditions, weight loss or gain of ≥ 7%, sedation, malnutrition/dehydration, and dysphagia. Significant risk factors for mortality in olanzapine-treated patients included age ≥ 80 years, concurrent benzodiazepine use, treatment-emergent sedation, and treatment-emergent pulmonary conditions. Additional analyses were performed to evaluate the effect of multiple risk factors. The presence of multiple risk factors (age ≥ 80, benzodiazepine use, treatment-emergent sedation, and treatment-emergent pulmonary conditions) had a significant impact on the incidence of mortality (these terms were used because incidence of mortality was increased in the olanzapine treatment group within each stratum [data not shown]). As the cumulative number of risk factors increased, incidence of mortality increased (0.7% mortality for patients with no risk factors, 1.5% for patients with 1 risk factor, 3.8% for patients with 2 risk factors, 18.7% for patients with 3 risk factors, and 30.0% mortality for patients with 4 risk factors; $p < .001$, Fisher exact test). Sex, baseline malnutrition/dehydration, baseline and treatment-emergent extrapyramidal symptoms, baseline body mass index, and baseline number of concomitant medications were not significant risk factors for mortality.

Organ system involvement at baseline and terminal event. Among the 49 patients in the integrated database who died, the metabolic system was the most common organ system involved at time of death in olanzapine-treated patients (N = 40/42, 95.2%), and the cardiac (N = 6/7, 85.7%) and metabolic systems (N = 6/7, 85.7%) were the most common systems affected in placebo-treated patients. Of all organ systems, the pulmonary system was the only organ system in which the percentage of patients who had pulmonary involvement at time of terminal event was higher than at baseline (baseline = 23.8%, N = 10/42; endpoint = 45.2%, N = 19/42) in olanzapine-treated patients. In placebo-treated patients, the percentage remained the same (14.3%, N = 1/7). Therefore, the narratives of patients with pulmonary system involvement at the time of the terminal event were reexamined in greater detail. This examination revealed that 2 of the 3 olanzapine-treated patients who had aspiration pneumonia at the time of the terminal event also had dysphagia prior to the development of pneumonia. In addition, a majority of olanzapine-

Figure 2. Meta-Analysis, Stratified by Protocol, of Exposure-Adjusted Incidence Rate Differences (IRDs) of Cerebrovascular Adverse Events in Olanzapine-Treated Patients From the 5 Double-Blind, Placebo-Controlled Clinical Trials and the Integrated Database[a]



[a]IRD values greater than zero indicate a higher incidence and those less than zero indicate a lower incidence of mortality in the olanzapine- than in placebo-treated patients. Confidence intervals not overlapping zero indicate a significant IRD between 2 treatment groups. Values for the integrated comparison used the fixed effects meta-analysis.
[b]p = .016.

treated patients with pulmonary system involvement in the terminal event also had immunologic compromise, malnutrition, sedation, dysphagia, or use of other medications known to be associated with sedation.

CVAEs

In the integrated database, the crude incidence of CVAEs was approximately 3 times higher in olanzapine- (1.3%, N = 15/1178) compared with placebo-treated patients (0.4%, N = 2/478), although when the data were pooled, this difference was not statistically significant (p = .177, Fisher exact test; see Table 2). However, the meta-analysis, stratified by protocol, demonstrated a significant non–exposure-adjusted incidence rate difference (IRD = 0.01, p = .031) and exposure-adjusted incidence rate difference (IRD = 0.39, p = .016), with a higher incidence in olanzapine- compared with placebo-treated patients. In the active comparator trials, there were no significant differences in the incidence of CVAEs between olanzapine- (2.5%, N = 5/204) and risperidone-treated patients (2.0%, N = 4/196; p = 1.0; HGGU) or olanzapine- (3.4%, N = 5/149) and conventional antipsychotic–treated patients (4.3%, N = 6/141; p = .765; HGGE; see Table 2). There were no significant differences in the exposure-adjusted incidence rates of CVAEs between olanzapine- and risperidone-, or olanzapine- and conventional antipsychotic–treated patients. Crude incidence rates for CVAEs from all 6 studies are presented by individual study in Table 2, and the individual exposure-adjusted incidence rate differences from the double-blind, placebo-controlled studies are presented in Figure 2. Types of CVAEs in olanzapine-, risperidone-, conventional antipsychotic–, and placebo-treated patients are presented in Table 5.

Age ≥ 80 years was significantly associated with an increased likelihood of experiencing a CVAE in patients in the integrated database (OR = 3.9, p = .01). A diagnosis of vascular or mixed dementia was also significantly associated with an increased likelihood of experiencing a CVAE in patients in the integrated database (OR = 5.6, p = .027) and in study HGGU (OR = 5.6, p = .014). In addition, a low baseline MMSE score (defined as a score of < 14) was significantly associated with an increased likelihood of experiencing a CVAE in patients in study HGGE (OR = 4.0, p = .033). Sex and treatment-emergent orthostatic hypotension were not significantly associated with an increased likelihood of CVAEs (p > .05). Sex and orthostatic hypotension were not significant risk factors for CVAEs in the integrated database, study HGGE, or study HGGU. The risk factors for CVAEs are presented in Table 6.

Treatment-Emergent Abnormal Laboratory Results

In the integrated database (excluding patients for whom data were unavailable), significantly more olanzapine- compared with placebo-treated patients experienced treatment-emergent abnormal changes in the following laboratory values at any time during treatment: low albumin (olanzapine 10.4%, N = 105/1006 vs. placebo 5.8%, N = 25/434, p = .002), low hematocrit (4.6%, N = 46/993 vs. 2.4%, N = 10/420; p = .05), low hemoglobin (4.2%, N = 43/1019 vs. 1.8%, N = 8/436; p = .028), and high prolactin levels (23.6%, N = 128/542 vs. 8.1%, N = 19/236; p < .001). Conversely, significantly fewer olanzapine-treated patients experienced treatment-emergent low alanine aminotransferase/serum glutamic-pyruvic transferase levels (0.4%, N = 4/1085, vs. 1.5% N = 7/460; p = .020), low chloride levels (0.2%, N = 2/1078 vs. 1.7%, N = 8/460; p = .002), and high monocyte levels (2.5%, N = 26/1036 vs. 4.8%, N = 21/438; p = .034) compared with placebo-treated patients from the integrated database at any time during treatment. A between-group comparison of olanzapine- and placebo-treated patients in these trials showed no statistically significant differences in mean changes or frequency of treatment-emergent abnormal changes in fasting glucose levels, nonfasting glucose levels, or fasting triglyceride levels. Baseline, endpoint, and mean changes in laboratory values are presented in Table 7.

Vital Signs

Olanzapine-treated patients gained significantly more weight during treatment (mean ± SD = 0.9 ± 3.4 kg; within-group p < .001) compared with patients treated with placebo (0.3 ± 2.5 kg; within-group p = .013; olanza-

Table 5. The Classification and Incidence of Cerebrovascular Adverse Events (CVAEs) in the Integrated Database, Study HGGU, and Study HGGE

Type of CVAE	Treatment Group	Crude Incidence N/N (%)	Crude p Value	Exposure-Adjusted Incidence[a]
Integrated database[b]				
Cerebrovascular accident	Olanzapine	9/1178 (0.8)	.30	27.0
	Placebo	1/478 (0.2)		7.4
Hemorrhagic stroke	Olanzapine	1/1178 (0.1)	1.00	3.0
	Placebo	0/478 (0.0)		0.0
Ischemic stroke NOS	Olanzapine	1/1178 (0.1)	1.00	3.0
	Placebo	0/478 (0.0)		0.0
Transient ischemic attack	Olanzapine	4/1178 (0.3)	1.00	12.0
	Placebo	1/478 (0.2)		7.4
Study HGGU				
Cerebrovascular accident	Olanzapine	3/204 (1.5)	1.00	59.0
	Risperidone	2/196 (1.0)		38.4
Transient ischemic attack	Olanzapine	2/204 (1.0)	1.00	39.4
	Risperidone	2/196 (1.0)		38.5
Study HGGE[c]				
Cerebrovascular accident	Olanzapine	2/149 (1.3)	.27	16.3
	Conventional antipsychotics	5/141 (3.5)		47.0
Transient ischemic attack	Olanzapine	1/149 (0.7)	1.00	8.2
	Conventional antipsychotics	1/141 (0.7)		9.4
Cerebral infarct	Olanzapine	2/149 (1.3)	.50	16.4
	Conventional antipsychotics	0/141 (0.0)		0.0

[a]Exposure-adjusted incidence rates, per 1000 patient-years.
[b]Excludes 6 patients in olanzapine group who were randomly assigned to, but did not receive, treatment.
[c]Excludes 1 patient in olanzapine group and 2 patients in conventional antipsychotic group who were randomly assigned to, but did not receive, treatment.
Abbreviation: NOS = not otherwise specified.

Table 6. Risk Factors Associated With Cerebrovascular Adverse Events (CVAEs) in all Elderly Patients With Dementia-Related Psychosis Treated With Olanzapine or Placebo in the Integrated Database

Risk Factor	CVAE[a] Yes	CVAE[a] No	CVAE[a] %	Odds Ratio	Risk Factor p Value[b]
Age, y[c]				3.88	.01
< 80	4	893	0.45		
≥ 80	13	763	1.70		
Sex				1.86	.21
Male	8	537	1.47		
Female	9	1119	0.80		
Mini-Mental State Examination score[c]				1.73	.08
< 14	6	783	0.76		
≥ 14	11	866	1.25		
Orthostatic hypotension[d]				1.36	.25
Yes	3	378	0.79		
No	14	1278	1.10		
Diagnosis				5.62	.03
Alzheimer's disease	14	1594	0.87		
Vascular/mixed dementia	3	62	4.62		

[a]The sample size for each risk factor varies, as the inclusion criteria for the analyses varied and not all patients had measurements of these variables after baseline.
[b]The p values were derived from a logistic regression analysis and determine if the odds ratio is significantly different from zero. For the risk factors, 5 separate models were analyzed, including treatment and the risk factor of interest.
[c]Baseline.
[d]Treatment emergent.

pine vs. placebo, $p < .001$). Significantly more olanzapine-treated patients experienced a treatment-emergent abnormal increase in weight ≥ 7% from baseline (17.2%, N = 196/1139 vs. 7.5%, N = 35/467 [excludes patients for whom data were unavailable]; $p < .001$). Baseline, endpoint, and mean changes in vital signs are presented in Table 7.

Other Adverse Events

In the analysis of the integrated database, significantly more olanzapine- than placebo-treated patients experienced treatment-emergent falls (12.4%, N = 147/1184 vs. 6.9%, N = 33/478; $p < .001$), somnolence (7.1%, N = 84/1184 vs. 2.9%, N = 14/478; $p < .001$), peripheral edema (5.2%, N = 61/1184 vs. 2.1%, N = 10/478; $p = .005$), abnormal gait (4.6%, N = 55/1184 vs. 2.1%, N = 10/478; $p = .017$), urinary incontinence (4.3%, N = 51/1184 vs. 1.9%, N = 9/478; $p = .019$), lethargy (4.1%, N = 48/1184 vs. 0.6%, N = 3/478; $p < .001$), asthenia (3.1%, N = 37/1184 vs. 1.3%, N = 6/478; $p = .039$), pyrexia (3.0%, N = 35/1184 vs. 0.6%, N = 3/478; $p = .003$), pneumonia (2.1%, N = 25/1184 vs. 0.6%, N = 3/478; $p = .035$), dry mouth (1.9%, N = 22/1184 vs. 0.4%, N = 2/478; $p = .023$), visual hallucinations (1.8%, N = 21/1184 vs. 0.4%, N = 2/478; $p = .035$), increased body temperature (1.4%, N = 16/1184 vs. 0.0%, N = 0/478; $p = .009$), increased weight (3.6%, N = 43/1184 vs. 1.7%,

Table 7. Baseline, Endpoint, and Mean Changes in Laboratory Values and Vital Signs in Olanzapine- and Placebo-Treated Patients From the Integrated Database

Parameter	Treatment Group	Baseline, mean ± SD	Endpoint, mean ± SD	Change, mean ± SD	Within-Treatment p Value[a]	Between-Treatment p Value[b]
Albumin (g/L)	Olanzapine	38.0 ± 3.9	37.1 ± 4.4	–0.8 ± 3.7	< .001	< .001
	Placebo	38.2 ± 3.8	38.1 ± 4.0	–0.2 ± 3.4	.54	
ALT/SPGT (U/L)	Olanzapine	17.7 ± 17.2	19.0 ± 18.2	1.3 ± 22.7	.01	.50
	Placebo	16.9 ± 8.3	17.5 ± 10.0	0.6 ± 9.4	.68	
Chloride (mmol/L)	Olanzapine	104.1 ± 3.5	104.9 ± 3.7	0.8 ± 3.7	< .001	< .01
	Placebo	104.2 ± 3.5	104.4 ± 3.6	0.2 ± 3.6	.26	
Cholesterol (mmol/L)	Olanzapine	5.4 ± 1.1	5.3 ± 1.1	–0.1 ± 0.7	< .001	.02
	Placebo	5.4 ± 1.0	5.4 ± 1.1	–0.03 ± 0.70	.17	
Glucose, fasting (mmol/L)	Olanzapine	5.6 ± 1.5	5.8 ± 1.7	0.2 ± 1.3	.19	.89
	Placebo	5.4 ± 1.2	5.6 ± 1.4	0.2 ± 1.2	.30	
Glucose, nonfasting (mmol/L)	Olanzapine	6.3 ± 2.4	6.5 ± 2.7	0.3 ± 2.6	< .001	.23
	Placebo	6.1 ± 2.4	6.2 ± 2.1	0.2 ± 2.2	.43	
Hematocrit (% of 1.0)	Olanzapine	40.0 ± 4.2	39.6 ± 4.5	–0.4 ± 3.6	< .001	< .01
	Placebo	40.0 ± 4.1	40.0 ± 4.4	–0.02 ± 3.20	.62	
Hemoglobin (mmol/L Fe)	Olanzapine	8.3 ± 0.9	8.2 ± 0.9	–0.1 ± 0.6	< .001	.03
	Placebo	8.3 ± 0.9	8.3 ± 0.9	–0.07 ± 0.60	< .01	
Hemoglobin, mean cell (COmmol/L Fe)	Olanzapine	20.7 ± 1.0	20.6 ± 1.0	–0.1 ± 1.1	< .01	.01
	Placebo	20.9 ± 1.0	20.7 ± 1.0	–0.2 ± 1.1	< .001	
Mean cell volume (fL)	Olanzapine	91.2 ± 5.9	91.1 ± 5.9	–0.1 ± 4.9	.25	.01
	Placebo	90.8 ± 6.1	91.2 ± 6.5	0.4 ± 4.2	.03	
Monocytes (GI/L)	Olanzapine	0.4 ± 0.2	0.4 ± 0.2	0.01 ± 0.20	.36	.17
	Placebo	0.5 ± 0.2	0.5 ± 0.2	–0.01 ± 0.20	.03	
Prolactin (mmol/L)	Olanzapine	0.6 ± 0.6	0.8 ± 0.7	0.2 ± 0.8	< .001	.06
	Placebo	0.8 ± 2.6	0.9 ± 3.0	0.1 ± 1.0	< .001	
Sodium (mmol/L)	Olanzapine	141.4 ± 3.0	142.1 ± 3.3	0.7 ± 3.5	< .001	< .01
	Placebo	141.0 ± 3.1	141.2 ± 2.9	0.1 ± 3.3	.48	
Triglycerides, fasting (mmol/L)[c]	Olanzapine	1.6 ± 1.1	1.5 ± 0.7	–0.1 ± 0.8	.39	.15
	Placebo	1.5 ± 1.0	1.6 ± 1.2	0.1 ± 0.7	.98	
Uric acid (μmol/L)	Olanzapine	296.4 ± 87.7	316.2 ± 95.7	19.8 ± 61.6	< .001	< .001
	Placebo	302.6 ± 85.2	312.0 ± 96.1	9.4 ± 55.0	< .001	
Urea specific gravity (g/cc)	Olanzapine	101.9 ± 0.7	101.8 ± 0.6	–0.1 ± 0.7	< .01	.02
	Placebo	101.9 ± 0.6	101.9 ± 0.6	0.03 ± 0.70	.55	
Pulse, supine (bpm)	Olanzapine	72.2 ± 10.0	72.4 ± 10.2	0.2 ± 10.6	.45	.73
	Placebo	72.3 ± 10.0	72.0 ± 9.9	–0.3 ± 10.6	.567	
Systolic blood pressure, supine (mm Hg)	Olanzapine	132.9 ± 17.7	131.4 ± 18.3	–1.6 ± 18.3	< .01	.21
	Placebo	133.5 ± 18.0	132.9 ± 17.4	–0.6 ± 18.4	.60	
Weight (kg)	Olanzapine	63.5 ± 14.0	64.4 ± 14.2	0.9 ± 3.4	< .001	< .001
	Placebo	63.7 ± 13.9	64.0 ± 14.1	0.3 ± 2.5	.01	

[a]Within-group p values are from Wilcoxon signed rank test on the mean change.
[b]Treatment p values are from Type III sum of squares from an analysis of variance model using terms for protocol and treatment.
[c]Study HGIV was the only study of the 6 that measured fasting triglyceride levels.
Abbreviation: ALT/SPGT = alanine aminotransferase/serum glutamic-pyruvic transferase.

8/478; p = .040), and erythema (1.0%, N = 12/1184 vs. 0.0%, N = 0/478; p = .024).

DISCUSSION

Olanzapine-treated patients had significantly higher rates of mortality compared with placebo-treated patients, but not compared with risperidone- or conventional antipsychotic–treated patients. The results of the present analysis are consistent with the FDA's finding that the mortality rates in elderly patients with behavioral disturbances associated with dementia treated with atypical antipsychotics are 1.6 to 1.7 times that of patients treated with placebo[1] and with a recently published meta-analysis.[25] The incidence of mortality in risperidone-treated patients in this analysis is similar to that reported by Brodaty and colleagues[26] (3.60%, N = 6/167 vs. 2.04%, N = 4/196 in this analysis). The incidence of mortality in olanzapine- and conventional antipsychotic–treated patients in study HGGE was higher than previously reported rates; yet, previous research suggests the incidence of mortality in elderly patients treated with atypicals (olanzapine or risperidone as 1 group = 4.75%, N = 61/1284) is lower than in elderly patients treated with haloperidol (21.4%, N = 64/299).[27] The dose of olanzapine was not associated with an increased incidence of mortality. Lower doses of olanzapine may be more effective than higher doses at reducing the behavioral disturbances associated with dementia,[15,20] but they are not associated with a lower risk of mortality.

Mortality rates in patients with dementia are high—almost twice that of the nondemented population[8]—

making dementia itself a risk factor for mortality. This analysis found several other risk factors for mortality, including age, a well-known risk factor for mortality[3,28] in elderly patients with dementia.[8,29] Treatment-emergent sedation was also a risk factor for mortality. Sedation and somnolence are commonly reported during treatment with olanzapine[30] and other atypical antipsychotics[10,26,31–33]; yet, 1 study reported somnolence rates as high as 25.3% in patients treated with placebo,[26] suggesting that sedation may be common in this population. However, in this analysis, treatment-emergent sedation occurred significantly more often in olanzapine- compared with placebo-treated patients. Sedation could lead to a lack of physical activity, which is also a risk factor for mortality in the elderly.[3] Concomitant benzodiazepine use may also cause sedation and was a significant risk factor for mortality in this analysis as well. However, elderly patients often use sedatives/hypnotics;[4] thus, avoiding concomitant use of benzodiazepines in this population may be difficult.

The emergence or worsening of a pulmonary condition was also a significant risk factor for mortality. Pulmonary conditions are prevalent in the elderly,[34,35] and pneumonia is the cause of death in a substantial number of patients with dementia.[35,36] Furthermore, dementia and a comorbid diagnosis of pulmonary conditions decreases survival rates.[37] Although significantly more olanzapine-treated patients experienced treatment-emergent pneumonia compared with patients treated with placebo, pulmonary conditions were a significant risk factor regardless of treatment, possibly reflecting an increased vulnerability in these patients. Moreover, the worsening of a pulmonary condition could reflect a progressive decline in health; in fact, a low baseline score on the MMSE (defined as a score of ≤ 18), was also a risk factor for mortality. This is consistent with previous research on the relationship between cognitive functioning and mortality in patients with dementia.[29] Because impaired functioning is a risk factor for both olanzapine- and placebo-treated patients and is associated with an increased risk for mortality in the elderly,[3] impairments in cognitive performance may be indicative of a decline in health for patients with dementia.

The nutritional indices of weight loss, dysphagia, malnutrition, and dehydration were all significant risk factors for mortality. Dysphagia[38] and dehydration[39] are common in the elderly and are risk factors for mortality. Moreover, the nutritional indices of low albumin and cholesterol levels are associated with an increased risk for mortality in the elderly.[28,40] In the present analysis, weight loss (or gain), dysphagia, malnutrition, and dehydration were all associated with an increased risk for mortality. However, van der Steen and colleagues[37] found that mortality rates were not associated with difficulty swallowing, weight loss, or dehydration, but rather, all 3 factors were associated with severity of dementia. Because these variables may be related, and because severity of dementia was also a risk factor for mortality in these patients, it is possible that these factors may indirectly contribute to the increased risk for mortality through their association with severity of dementia. Orthostatic hypotension was not a significant risk factor for CVAEs in this analysis. Past research has found that orthostatic hypotension is a risk factor for CVAEs in the elderly[41] and other populations[42] and is thought to be one of the potential mechanisms behind the potential link between atypical antipsychotics and CVAEs.[43]

The findings regarding organ system involvement at terminal event in olanzapine-treated patients are similar to the findings of previous studies in elderly patients and elderly patients with dementia.[9,35,37,38] Moreover, these findings are consistent with the FDA's recent findings that, although the cause of death varied, most deaths were either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia).[1] This is especially true for pulmonary conditions,[35,37,38] which are associated with an increased risk for mortality in elderly patients with dementia.[38] A closer examination of patients with pulmonary conditions in this analysis suggested potential associations between aspiration pneumonia and dysphagia and between pulmonary conditions and malnutrition or sedation. This is consistent with the previous findings that both sedation and malnutrition are risk factors for mortality, and dysphagia and malnutrition[40] are risk factors for pneumonia.

In addition to higher rates of mortality, the incidence of CVAEs in olanzapine-treated patients was approximately 3 times that of patients treated with placebo. There were no significant differences between olanzapine-treated patients compared with those treated with risperidone or conventional antipsychotics. The incidence of CVAEs in risperidone-treated patients in this analysis is similar to rates reported in the Brodaty et al. study[26] but is inconsistent with the findings of Katz and colleagues,[32] who reported no occurrences of CVAEs. As with mortality, antipsychotics have relatively similar safety profiles with regard to CVAEs.[43–45] However, elderly patients with behavioral disturbances associated with dementia treated with antipsychotics have an elevated risk for CVAEs, given both the potential association between treatment with these drugs and CVAEs[43–45] and the finding that patients with dementia have more severe cerebrovascular disease than patients without dementia.[9]

The risk factors for CVAEs in this population (≥ 80 years of age, a diagnosis of vascular or mixed dementia, and cognitive impairment) are similar to the CVAE risk factors of the general population.[46] Age was found to be a significant risk factor, consistent with previous studies in elderly patients with dementia.[47] Similarly, a diagnosis of mixed or vascular dementia was associated with a 5-fold greater likelihood of developing a CVAE compared with a diagnosis of Alzheimer's disease. This agrees with the

finding that approximately one fifth of stroke patients will experience a subsequent CVAE.[9] Finally, cognitive impairment was a risk factor for CVAEs, which is also consistent with previous research.[47] Because some of the risk factors for CVAEs are also risk factors for mortality, clinicians should carefully consider treatment options when these risk factors are present.

In addition to mortality and CVAEs, treatment-emergent low albumin, low hematocrit, low hemoglobin, and high prolactin were also significantly more likely in olanzapine-treated patients than placebo-treated patients. The increases in prolactin are consistent with previous research in elderly patients with schizophrenia treated with olanzapine[7,48] and risperidone.[7] Weight gain of greater than or equal to 7% of baseline occurred more often in olanzapine- than in placebo-treated patients. Although patients in both groups gained weight during treatment, patients treated with olanzapine gained more weight. Because the weight gain in these patients is relatively small (0.82 kg in olanzapine-treated patients in the present study vs. 4.1 kg in younger patients without dementia in a separate 28-week study)[49] and elderly patients are at risk for malnutrition,[40,50] weight gain in this population may not be as much of a concern as in younger patients.

Significantly more olanzapine- than placebo-treated patients experienced abnormal gait, asthenia, dry mouth, erythema, increased weight, increased body temperature, lethargy, peripheral edema, pyrexia, somnolence, and visual hallucinations. Most of these adverse events are consistent with the known safety profile of olanzapine. In addition, olanzapine-treated patients experienced significantly more occurrences of pneumonia, falls, and urinary incontinence. Falls are common in elderly patients and in elderly patients taking antipsychotics[10,26,33] and may have several potential causes, including postural instability, which has been reported during olanzapine treatment in patients with Alzheimer's disease[30,48]; dizziness, which has been reported in elderly patients with schizophrenia treated with olanzapine[6,48] and risperidone[33]; sedation, reported in olanzapine- and risperidone-treated elderly patients with schizophrenia[33,48]; and/or orthostatic hypotension, which has been reported during olanzapine[30] and risperidone[33] treatment. Falls are also common in placebo-treated patients with dementia, occurring in 27.1% of patients (N = 46/170) in 1 study,[26] suggesting that the elderly may be susceptible to falls, in general. Urinary incontinence occurred significantly more often in olanzapine- than in placebo-treated patients and is common in the elderly, elderly patients with dementia, and elderly patients with a history of CVAEs;[51] yet, it is a serious problem because of its association with decreased survival rates.[36]

The limitations of this analysis include the integration of data from several studies with patients who were relatively similar in diagnosis and age but received different doses of olanzapine for different lengths of time. Three of the analyzed studies used flexible dosing schedules, and the other 3 used fixed dosing schedules. Thus, if patients were unable to tolerate the prescribed dose in the fixed studies, they were discontinued from the study. Similarly, differences in the lengths of these studies may have led to an underestimation of adverse events, as the duration of HGEU was 6 weeks (with an 18-week open-label extension phase), and the duration of study HGGE was 59 weeks. Furthermore, although the studies were composed of similar populations, there were some differences. For example, studies HGAO, HGEU, HGIC, and HGIV consisted only of patients with a diagnosis of Alzheimer's disease, and the other studies included a mix of diagnoses, including mixed and vascular dementias (HGGU), as well as other psychotic disorders (HGGE). However, a vast majority of the patients in each trial had a diagnosis of Alzheimer's disease, with the least being 60.0% in HGGE.

CONCLUSION

While several reports on the use of antipsychotics in elderly patients with dementia are available,[4,10,11] this is the first integrated analysis focusing on adverse events in these patients. Antipsychotics are not approved for the treatment of dementia in the United States, and the FDA has recently issued a "black box" warning indicating an increased risk of mortality among elderly patients with behavioral disturbances associated with dementia treated with atypical antipsychotics compared with patients treated with placebo.[1]

Approximately half of patients with dementia suffer from psychosis and agitation, which is also the primary cause of institutionalization for this population.[52] The use of antipsychotics in elderly patients with behavioral disturbances associated with dementia necessitates a careful assessment of the benefits and potential risks associated with each treatment, especially given the increased risk for mortality[1,27] and CVAEs.[43,44] The patient's condition and the acute nature of the symptoms require prompt and effective action to ameliorate the behavioral disturbances and bring the symptoms under control; yet, the delicate balance between the fragility of the patient and the problems associated with comorbid conditions, concomitant medications, and the increased risk of adverse events requires a cautious approach to drug selection and dosing. Olanzapine's label recommends caution in treating elderly patients, especially when factors affecting drug metabolism or pharmacodynamic sensitivity are present.

The recent "black box" warning issued by the FDA for use of atypical antipsychotics has raised additional concerns for clinicians.[1] This article will hopefully provide additional useful information to clinicians so they can better understand the potential risks of antipsychotic treatment in these patients and educate their patients and patients' caregivers about the risks and benefits of atypical

antipsychotic treatment. Prescribers should carefully consider the potential risks during treatment with oral olanzapine and other antipsychotics in this patient population, especially when risk factors for mortality and CVAEs are present.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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