A Double-Blind Comparison of Olanzapine Versus Risperidone in the Acute Treatment of Dementia-Related Behavioral Disturbances in Extended Care Facilities

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Background: In addition to demonstrating their superiority to placebo, there is a need to compare the relative efficacy and side effects of atypical neuroleptics for the acute treatment of dementia-related behavioral disturbances in residents of long-term care facilities.

Method: In a double-blind parallel study allowing dose titration over 14 days, 39 agitated persons with DSM-IV dementia who were residing in long-term care facilities were administered olanzapine (N = 20) or risperidone (N = 19) as acute treatment. Drug was administered once a day at bedtime. The initial dosages were olanzapine, 2.5 mg/day, and risperidone, 0.5 mg/day. Titration was allowed to maximum doses of olanzapine, 10 mg/day, and risperidone, 2.0 mg/day. The primary outcome measures were the Clinical Global Impressions scale (CGI) and the Neuropsychiatric Inventory (NPI). Data were gathered from 2000 to 2002.

Results: Both drugs produced significant reductions in CGI and NPI scores ($p < .0001$), but there was no significant difference between drugs. The mean olanzapine dose was 6.65 mg/day; for risperidone, the dose was 1.47 mg/day. The positive drug effect was not accompanied by decreased mobility, and there was improvement on a quality-of-life measure. The chief adverse events were drowsiness and falls. At baseline, 42% (16/38) of subjects in both groups had extrapyramidal symptoms that increased slightly, but not significantly, by the end of the study.

Conclusion: Low-dose, once-a-day olanzapine and risperidone appear to be equally safe and equally effective in the treatment of dementia-related behavioral disturbances in residents of extended care facilities.

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Atypical neuroleptics are used widely for the management of dementia-related behavioral disturbances in long-term care facilities. There is evidence that they are more effective than placebo,[1–3] but there have been no head-to-head comparisons of these drugs to determine their relative efficacy. The investigators report a head-to-head blinded study of olanzapine versus risperidone for the acute treatment of behavioral disturbance in elderly persons with dementia residing in long-term care facilities.

METHOD

Selection of Subjects

Because there were no data available for estimating sample size at the beginning of this study, an arbitrary sample size of 20 subjects per group was selected. All subjects resided in extended care facilities. All met DSM-IV criteria for dementia. They were medically stable and able to comply with oral, nonliquid medication. Informed consent or assent was obtained from each subject and a family member using forms approved by the University of Texas Southwestern Medical Center Institutional Review Board. We required a Clinical Global Impressions scale[4] (CGI) score ≥ 4 and an Alzheimer's Disease Cooperative Study (ADCS) agitation screening scale[5] score ≥ 25 with 6 points on the delusions, hallucinations, physical aggression, or verbal aggression subscales. We allowed ongoing use of anticonvulsants (except for carbamazepine), anti-

depressants, and cholinesterase inhibitors if they had been in stable use for 30 days prior to drug washout. We also allowed episodic use of antiemetics; cough/cold preparations (except those containing diphenhydramine); inhaled, topical, or ophthalmic steroids; zolpidem; and chloral hydrate. Lorazepam was allowed in doses of 0.5 to 1 mg p.o. as needed for acute agitation.

Exclusions

We excluded persons with previous neuroleptic malignant syndrome or known sensitivity to olanzapine or risperidone. We also excluded persons with current major depressive disorder or history or evidence of schizophrenia or bipolar disorder. Also excluded were persons receiving amantadine, anorexics, carbamazepine, chloramphenicol, clonidine, erythromycin, guanabenz, guanadrel, guanethidine, guanfacine, ketanserin, methyldopa, metyrosine, narcotics, psychostimulants, reserpine, tryptophan, antiparkinsonian drugs, and benzodiazepines other than lorazepam.

Study Design

The study was a double-blind 2-week titration parallel study of olanzapine versus risperidone with allowance for increasing and decreasing the dosage of both medications. After a 3-day washout of psychotropic drugs (stable doses of mood stabilizers and antidepressants were allowed), patients were dosed with olanzapine, 2.5, 5.0, or 10.0 mg p.o. h.s., or risperidone, 0.5, 1.0, or 2.0 mg p.o. h.s., over a 14-day period of time. Increases were allowed on days 2, 3, and 8 at increments of 2.5 mg for olanzapine and 0.5 mg for risperidone. Dosage decreases were allowed at any visit. During the washout period, chloral hydrate, 500 mg p.o., and lorazepam, 1 mg p.o., were used as rescue medications.

Outcome Measures

The primary outcome measures were the Neuropsychiatric Inventory[6] (NPI) and the CGI. Secondary efficacy measures were the Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale[7] (E-BEHAVE-AD), the Psychogeriatric Dependency Rating Scales[8] (PGDRS), the Multidimensional Observational Scale for Elderly Subjects[9] (MOSES), the Mini-Mental State Examination[10] (MMSE), and the Quality of Life in Late-Stage Dementia Scale[11] (QUALID). Safety measures included the Abnormal Involuntary Movement Scale[12] (AIMS), the Barnes Akathisia Scale,[13] and the Simpson-Angus Scale[14] for extrapyramidal symptoms (EPS).

The CGI is a 7-point global assessment of emotional/behavioral disturbance at the time of examination. The NPI is a 12-item scale that assesses psychopathology and behavioral disturbance in persons with dementing illness in terms of both frequency and severity of symptoms; the rating is for the previous week. The E-BEHAVE-AD is a 12-item scale that rates severity of psychopathology and behavioral disturbance in persons with dementing illness at the time of clinical examination. The PGDRS is a global score for elders that includes orientation, behavioral disturbance, and competence at activities of daily living. The MOSES is an 8-item scale rating social behaviors over the 7 previous days. The MMSE is a 30-point scale measuring global cognitive function, and the QUALID is an 11-point rating of items observed over 7 days that are related to quality of life. Ratings on the CGI, E-BEHAVE-AD, MMSE, AIMS, Simpson-Angus Scale, and Barnes Akathisia Scale are made on the basis of direct observation and testing by a clinician. The NPI, MOSES, PGDRS, and QUALID were administered to a nurse or nurse aide familiar with the patient. In addition to baseline observations, patients were also observed on days 1, 2, 3, 5, 8, 10, 12, and 15 of the study by the study nurse and the study physician. Data were gathered from 2000 to 2002.

Statistical Measures

Baseline measures for the 2 drug groups (olanzapine and risperidone) were compared using t tests for continuous measures and either the chi-square or Fisher exact test for categorical measures. All continuous outcome measures were analyzed using a 2-factor analysis of variance with a between factor (drug group) and a repeated factor (first visit [baseline visit, visit 1, or visit 2 depending on measure] vs. visit 9). All categorical outcome measures (visit by group by outcome) were examined using both Mantel-Haenszel tests and Breslow-Day tests for homogeneity.

RESULTS

Forty-seven subjects were recruited into the study. A total of 39 subjects were randomly assigned to treatment; 20, to the olanzapine group and 19, to the risperidone group. They are described in Table 1. Subjects were assigned a DSM-IV diagnosis on the basis of clinical examination, history from the nursing home chart or a knowledgeable informant, and previous diagnosis recorded in the nursing home record. Diagnoses included Alzheimer's disease (35), vascular dementia (1), dementia due to viral encephalitis (1), dementia due to subdural hematoma (1), and dementia not otherwise specified (1). Of these subjects, 7/20 (35%) of the olanzapine group and 6/19 (32%) of the risperidone group were receiving neuroleptics. Pretrial psychotropic drug use is indicated in Table 2.

On the last day of the trial, 16/20 olanzapine and 17/19 risperidone patients were still receiving study drug. The mean daily dose of olanzapine was 6.65 mg (range, 2.5–10 mg; modal dose = 10 mg). Olanzapine was discontinued in 4 subjects: in 1 subject, due to a rash accompanied by elevated blood pressure, pulse, white blood cell count, and temperature; in 2, because of unsteady gait or falls; and in 1 because of diaphoresis, fainting, and asys-

Table 1. Characteristics of the Olanzapine and Risperidone Groups at Baseline

Characteristic	Olanzapine (N = 20)	Risperidone (N = 19)	p Value
Gender (female), N (%)	12 (60)	14 (74)	.36
Age, mean ± SD, y	83.3 ± 5.7	83.0 ± 9.4	.90
White, %	90.0	84.2	.60
MMSE score, mean ± SD	7.2 ± 7.0	9.3 ± 7.2	.36
Agitation (ADCS screening scale) score, mean ± SD	37.9 ± 10.2	34.4 ± 10.3	.30
Sitting heart rate, mean ± SD	80.7 ± 10.9	80.7 ± 8.3	> .99
Sitting systolic BP, mean ± SD, mm Hg	131.5 ± 18.8	132.4 ± 19.9	.89
Sitting diastolic BP, mean ± SD, mm Hg	73.7 ± 11.6	77.5 ± 10.5	.31

Abbreviations: ADCS = Alzheimer's Disease Cooperative Study, BP = blood pressure, MMSE = Mini-Mental State Examination.

Table 2. Psychotropic Drug Use Prior to Study, N (%)

Type of Psychotropic	Both Groups (N = 39)	Olanzapine (N = 20)	Risperidone (N = 19)	p Value
Antianxiety	27 (69)	13 (65)	14 (74)	.56
Anticonvulsant	7 (18)	5 (25)	2 (11)	.41[a]
Antidepressant	16 (41)	5 (25)	11 (58)	.04
Antidepressant, sedating	8 (21)	5 (25)	3 (16)	.70[a]
Antipsychotic	13 (33)	7 (35)	6 (32)	.82
Cholinesterase inhibitor	8 (21)	3 (15)	5 (26)	.45[a]
Hypnotic	3 (8)	3 (15)	0 (0)	.23[a]

[a]Indicates that the Fisher exact test was used. For all other values, the chi-square test was used.

tole. Olanzapine dose was reduced but not discontinued in 3 patients. The mean daily dose of risperidone was 1.47 mg (range, 0.5–2 mg; modal dose = 2 mg). Risperidone was not discontinued in any patient (in 1 subject, drug was withheld on day 14 because of a fall, and in another subject, the nurse failed to administer the drug on days 10–14). Risperidone dosage reductions were made in 8 patients for drowsiness (4), dystonia (1), mild EPS (2), and falls (1). From day 1 to day 15 of the study, lorazepam was administered to 11/20 (55%) of the olanzapine-treated subjects (mean total dose = 3.84 mg) and to 10/19 risperidone-treated subjects (53%) (mean total dose = 3.35 mg).

Scores on the ADCS screening scale showed no difference in levels of behavioral disturbance at screening or baseline (see Table 1). Scores for the various outcome measures are presented in Table 3. Total NPI scores (frequency × severity) were significantly reduced by both drugs ($F = 21.25$, $df = 1,36$; $p < .0001$), as were scores on the depression/dysphoria subscale ($F = 5.26$, $df = 1,36$; $p = .0277$); the anxiety subscale ($F = 11.63$, $df = 1,36$; $p = .0016$); the combined agitation, disinhibition, irritability, and aberrant motor behavior subscales ($F = 25.87$, $df = 1,36$; $p < .0001$); and the combined delusions/hallucinations subscales ($F = 4.14$, $df = 1,36$; $p = .0492$). No differences between drugs appeared on any of the foregoing scales. The NPI appetite subscale was found to have a significant interaction of visit by drug group ($F = 4.11$, $df = 1,36$; $p = .0501$); while the risperidone group was higher (1.79 points) than the olanzapine group at visit 2, the olanzapine group was slightly higher (0.11 points) than the risperidone group at visit 9. The CGI showed significant reduction for both groups ($F = 67.32$, $df = 1,36$; $p < .0001$), but no difference between drugs.

For both drugs, there was significant reduction of global E-BEHAVE-AD scores ($F = 12.714$, $df = 1,36$; $p = .001$) and the sum of all subscale scores ($F = 5.797$, $df = 1,36$; $p = .021$) on day 14 and a significant difference between drugs for the sum of all subscale scores ($F = 5.787$, $df = 1,36$; $p = .021$). The mean change in sum was higher in the olanzapine group. There was significant reduction in the behavioral scores of the PGDRS ($F = 18.496$, $df = 1,36$; $p < .001$), but no difference between drugs. There was essentially no change in scores on the orientation or physical mobility scales of the PGDRS, indicating that the calming effects of the drugs were not at the cost of decreased mobility or increased confusion. The latter was confirmed by MMSE scores, which were unchanged from baseline on day 14. There was also no significant change in MOSES scores for either group. QUALID scores showed significant improvement for both drugs ($F = 5.23$, $df = 1,29$; $p = .03$).

The 2 groups did not differ in weight at baseline, and no significant change was seen in weight with either drug over the 14 days of the trial. Heart rate and blood pressure measurements did not differ between groups at baseline or end of study except that the olanzapine group had higher pulse pressure at the beginning and end of the study ($F = 4.368$, $df = 1,21$; $p = .049$). There was also no significant difference between groups in standing diastolic blood pressure at baseline or end of study. As would be expected in this frail population, adverse events were frequent. A total of 113 adverse events were recorded for the 31 patients who had at least 1 adverse event. One patient in the olanzapine group had 2 serious adverse events: an episode of asystole (at which time olanzapine was withdrawn) followed 6 days later by a brain stem stroke. Adverse events were similar in both groups. There were 12 falls; 2 were the result of being pushed by other patients. Of the 10 spontaneous falls, 4 occurred in the group that received lorazepam (2 olanzapine, 2 risperidone), and 6 in the group receiving atypical antipsychotics alone (4 olanzapine, 2 risperidone). There was no significant association between falls and use of lorazepam ($p = .47$, Fisher exact test [2-sided]) and no difference in falls between olanzapine and risperidone ($p = .62$, Fisher exact test [2-sided]).

At baseline, 42% (16/38) of patients in both drug groups had EPS (combined resting tremor, bradykinesia, and cogwheel rigidity) on neurologic examination. (EPS data were missing for 1 patient.) There was a trend toward

Table 3. Outcome of Treatment With Olanzapine or Risperidone by Group[a]

	Olanzapine		Risperidone		
Scale	Baseline	Day 15	Baseline	Day 15	p Value
CGI	4.63 ± 0.76	3.32 ± 1.06	4.68 ± 0.89	3.42 ± 1.07	< .0001[b] .77[c] .87[d]
NPI (frequency × severity)	45.89 ± 25.02	30.89 ± 19.59	57.79 ± 23.65	34.16 ± 17.41	< .0001[b] .19[c] .31[d]
E-BEHAVE-AD					
Global score	1.26 ± 0.99	1.47 ± 1.02	0.37 ± 0.60	0.89 ± 1.10	.001[b] .11[c] .45[d]
Total score	4.05 ± 3.66	1.79 ± 2.30	6.74 ± 6.10	4.89 ± 5.17	.02[b] .02[c] .81[d]
PGDRS					
Behavioral symptoms	14.05 ± 5.97	10.00 ± 5.57	16.00 ± 4.88	11.74 ± 6.70	< .001[b] .26[c] .91[d]
Orientation	5.42 ± 2.71	5.21 ± 2.92	5.53 ± 2.46	6.00 ± 2.58	.69[b] .58[c] .30[d]
Mobility	3.05 ± 1.65	2.89 ± 1.76	3.68 ± 1.57	3.68 ± 1.57	.07[b] .19[c] .07[d]
MOSES	22.42 ± 5.49	21.68 ± 6.39	22.11 ± 3.63	20.37 ± 5.69	.18[b] .59[c] .59[c]
QUALID	30.75 ± 6.59	26.69 ± 9.17	31.13 ± 7.77	27.60 ± 8.01	.03[b] .78[c] .88[d]
Simpson-Angus Scale	1.25 ± 0.39	1.42 ± 0.51	1.39 ± 0.60	1.51 ± 0.45	.08[b] .44[c] .73[d]
AIMS rating of minimal to mild, N (%)[f]	3 (17)	3 (17)	2 (11)	1 (6)	.52[e]
BAS rating of questionable or mild symptoms, N (%)[f]	1 (6)	2 (11)	1 (6)	1 (6)	ND

[a]Values are shown as mean ± SD unless otherwise noted.
[b]Visit effect (analysis of variance).
[c]Drug group effect (analysis of variance).
[d]Visit-by–drug group interaction effect (analysis of variance).
[e]Breslow-Day homogeneity test of the odds ratios.
[f]Visit 9 data for these measures are missing for 1 risperidone and 1 olanzapine patient. Another patient in the olanzapine group died during the study, and data for visits 4–9 are missing.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, CGI = Clinical Global Impressions scale, E-BEHAVE-AD = Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale, MOSES = Multidimensional Observational Scale for Elderly Subjects, ND = not done (homogeneity tests could not be performed due to too few frequencies), NPI = Neuropsychiatric Inventory, PGDRS = Psychogeriatric Dependency Rating Scales, QUALID = Quality of Life in Late-Stage Dementia Scale.

increase in Simpson-Angus Scale scores that did not reach significance ($F = 3.36$, $df = 1,34$; $p = .08$). Both drug groups were found to have similar responses ($p = .52$, Breslow-Day) on the AIMS when the none/normal category was compared with the minimal and mild categories (no response was above "mild") at visits 2 and 9. On the Barnes Akathisia Scale, 15/18 patients in the olanzapine group and 16/18 patients in the risperidone group had "absent" responses for both visits 2 and 9, with no responses above "mild" (too few responses above the "absent" response for a test).

We considered the possibility that the use of lorazepam as a rescue medication might have influenced the outcome of the study. The median number of days of lorazepam administration was 3.5 (range, 1–12), and the median dose of lorazepam was 2 mg (range, 0.2–21 mg). No significant difference was found in scores on total NPI, E-BEHAVE-AD, or global E-BEHAVE-AD in the group that received more than 2 doses of lorazepam and the group that received 2 or fewer doses.

DISCUSSION

Both olanzapine and risperidone administered once a day were similarly effective in the acute treatment of behavioral symptoms associated with dementing illness

in frail, elderly residents of long-term care facilities. Side effect profiles of olanzapine at a mean dose of 6.65 mg/day and risperidone at a mean dose of 1.47 mg/day were similar. Adverse events were frequent and largely mild. The most frequent were drowsiness, falls, and EPS. EPS, however, did not increase greatly over baseline on the Simpson-Angus Scale, and there was no significant change in the mobility subscale of the PGDRS with either drug. Drug discontinuation and dose reduction occurred in roughly equal numbers of patients in both groups, with drug discontinuation more common in the olanzapine group and dose reduction more common in the risperidone group. Although it would have been more desirable not to allow the use of a rescue medication, it was necessary to ensure the cooperation of the nursing staff and for the safety and comfort of patients, and it did not appear to affect the outcome of the study.

Given the severity of patients' cognitive impairment, it is not surprising that there was no change in MOSES score; this instrument assesses items such as interest in others and in outside events. By contrast, the more favorable scores on the QUALID indicate that the behavioral improvements did not come at the cost of decreased quality of life.

Drug names: amantadine (Symmetrel and others), carbamazepine (Carbatrol, Tegretol, and others), chloramphenicol (Chloromycetin, Chloroptic, and others), clonidine (Catapres and others), diphenhydramine (Benadryl and others), erythromycin (Erygel, Eryderm, and others), guanabenz (Wytensin and others), guanfacine (Tenex and others), lorazepam (Ativan and others), methyldopa (Aldomet and others), metyrosine (Demser), olanzapine (Zyprexa), reserpine (Serpalan and others), risperidone (Risperdal), zolpidem (Ambien).

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