Comparison of Risperidone and Placebo for Psychosis and Behavioral Disturbances Associated With Dementia: A Randomized, Double-Blind Trial

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Background: We report the findings from the first large, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of risperidone in the treatment of psychotic and behavioral symptoms in institutionalized elderly patients with dementia.

Method: 625 patients (67.8% women; mean age = 82.7 years) with DSM-IV diagnoses of Alzheimer's disease (73%), vascular dementia (15%), or mixed dementia (12%) and significant psychotic and behavioral symptoms were included. Each patient was randomly assigned to receive placebo or 0.5 mg/day, 1 mg/day, or 2 mg/day of risperidone for 12 weeks. The primary outcome measure was the Behavioral Pathology in Alzheimer's Disease rating scale (BEHAVE-AD).

Results: The study was completed by 70% of the patients. Baseline Functional Assessment Staging scores were 6 or 7 in more than 95% of the patients, indicating severe dementia. At endpoint, significantly greater reductions in BEHAVE-AD total scores and psychosis and aggressiveness subscale scores were seen in patients receiving 1 and 2 mg/day of risperidone than in placebo patients ($p = .005$ and $p < .001$, respectively). At week 12, 0.5 mg/day of risperidone was superior to placebo in reducing BEHAVE-AD aggression scores ($p = .02$). More adverse events were reported by patients receiving 2 mg/day of risperidone than 1 mg/day. The most common dose-related adverse events were extrapyramidal symptoms, somnolence, and mild peripheral edema. The frequency of extrapyramidal symptoms in patients receiving 1 mg/day of risperidone was not significantly greater than in placebo patients.

Conclusion: Risperidone significantly improved symptoms of psychosis and aggressive behavior in patients with severe dementia. Results show that 1 mg/day of risperidone is an appropriate dose for most elderly patients with dementia.

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Late-life dementias are associated not only with deficits in cognition and self-care, but also with noncognitive psychiatric and behavioral symptoms, including delusions, hallucinations, aggression, and agitation.[1–8] These symptoms, which are observed in up to 90% of patients with dementia,[9] are important targets for evaluation and intervention because they may be more responsive to available treatments than are cognitive and functional deficits, and because they can contribute to patients' distress, caregivers' burden, and the need for nursing home placement. Today, the best documented pharmacologic agents for these symptoms are antipsychotic medications.[10] Use of conventional antipsychotics, however, has been limited by side effects such as falls, hypotension, sedation, and extrapyramidal symptoms, as well as tardive dyskinesia. Concern over the risks versus the benefits of antipsychotic medications in American nursing homes was among the factors that led to the passage of the nursing home reform provisions of the Omnibus Budget Reconciliation Act of 1987 (Public Law 100-203).

In recent years, newer antipsychotic agents, combined serotonin and dopamine antagonists, have been developed that appear to have a more benign side effect profile than the conventional agents. Case studies[11,12] of elderly patients with dementia suggest that risperidone, one of the newer agents, may reduce delusions, aggression, and agitation without severe extrapyramidal symptoms or agitation and that such treatment may improve participation in social activities. An open study[13] of 109 nursing home residents found risperidone to be safe and effective in

treating dementia-related behavioral symptoms. Motivated by both clinical and public policy questions about the efficacy and safety of the newer antipsychotic medications, we pursued these preliminary findings by conducting a placebo-controlled, double-blind study of risperidone for the treatment of psychosis and aggression in a large sample of long-term care patients with dementia.

METHOD

Patient Selection

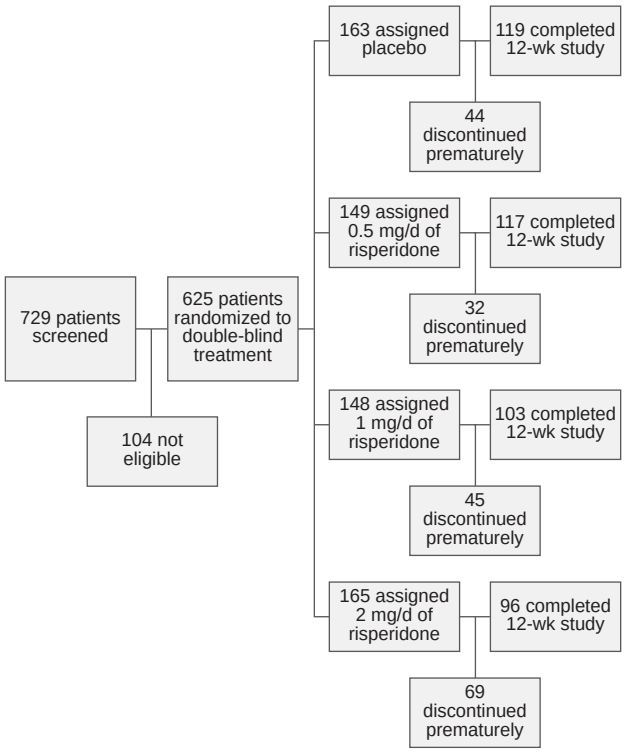
Patients were required to be 55 years or older, to reside in a nursing home or chronic disease hospital, and to have *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[14] (DSM-IV) diagnoses of Alzheimer's disease, vascular dementia, or a combination of the two, with scores of 4 or greater on the Functional Assessment Staging rating scale[15] and 23 or lower on the Mini-Mental State Examination.[16] They were required to have a total score ≥ 8 and a global rating ≥ 1 on the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale,[17] indicating significant psychotic and behavioral symptoms. Excluded were patients with untreated reversible causes of dementia, patients with medical or neurologic conditions that diminish cognition, patients with a diagnosis of dementia related to infection with the human immunodeficiency virus or substance-induced persistent dementia, patients with a diagnosis of delirium or amnestic disorder, and patients with a psychiatric diagnosis that could have accounted for the observed psychotic disturbances. Institutional review board approval was obtained at each study site, and every patient and his/her family member or health care proxy gave written informed consent before participating. The study conformed with the Declaration of Helsinki.

Design

Patients were randomly assigned according to a randomization code provided by the sponsor (Janssen Research Foundation). Identically appearing risperidone (0.25, 0.5, and 1.0 mg) and placebo tablets were supplied by the sponsor. Each patient received 2 tablets twice daily. All trial drugs were appropriately labeled with a 2-part label containing the visit, protocol, patient numbers, and directions for administration. The first part of the label remained attached to the medication carton and the second part (double-blind portion) was detached and placed in the case report form.

After a single-blind placebo washout period of 3 to 7 days, eligible patients were randomly assigned to placebo or to 0.5, 1.0, or 2.0 mg/day of risperidone, administered in divided doses (morning and bedtime) for 12 weeks (Figure 1). Doses for patients receiving 1.0 mg/day and 2.0 mg/day were adjusted during the first double-blind week in increments of 0.5 mg/day every 2 days. Concomitant use of antipsychotics, antidepressants, or mood stabilizers was not allowed. Benztropine was allowed to treat extrapyramidal symptoms. Lorazepam (up to 3 mg/day for up to 4 days in any 7-day period) could be given until the end of week 4. Use of chloral hydrate for insomnia was allowed at the lowest effective dose.

Figure 1. Trial Profile



Efficacy was evaluated using the BEHAVE-AD rating scale, the Cohen-Mansfield Agitation Inventory,[18] and the Clinical Global Impressions scale[19] at selection, baseline, and weeks 1–4, 6, 8, 10, and 12 (or when the patient was terminated from treatment). This information was elicited from the patients' primary caregivers by specifically trained raters. The primary efficacy measure was the BEHAVE-AD total score. To provide data on categorical responses, in this article we used a post hoc criterion of a 50% reduction in BEHAVE-AD total scores. The BEHAVE-AD is a 25-item scale that measures the severity of behavioral disturbances on 4-point scales in 7 major categories (Appendix 1). The psychosis subscale is the sum of the paranoid/delusional ideation and hallucinations subscales. The reliability of the BEHAVE-AD has been demonstrated in both outpatients and nursing home residents.[20] The Cohen-Mansfield Agitation Inventory rates the frequency of 29 agitated behaviors in 4 factors on 7-point scales. The items included in the physically and verbally aggressive factors are also listed in Appendix 1. The Clinical Global Impressions scale is a physician-rated 7-point

scale with ratings ranging from normal (1) to extremely severe (7). Cognitive performance and functional status were determined at baseline and week 12 using the Mini-Mental State Examination and Functional Assessment Staging. Basic activities of daily living were evaluated at every visit using the Physical Self-Maintenance Scale.[21]

Vital signs and information regarding adverse events were obtained at each visit. Electrocardiograms were obtained at baseline and weeks 4 and 8. Clinical laboratory tests were performed at baseline and weeks 4, 8, and 12. Physical and neurologic examinations were conducted at baseline and week 12 (or termination). Severity of extrapyramidal symptoms was monitored at each visit with the Extrapyramidal Symptom Rating Scale.[22]

Sample size calculations were performed using models on which an alpha level of .0167 was used to adjust for multiple comparisons between each risperidone group (0.5, 1, and 2 mg/day) versus placebo. Thus, to detect a difference of 20% in response rates between at least one risperidone group and placebo at an overall alpha level of .05 with 80% power, at least 119 patients per group were required.

Statistical Analysis

Endpoint analyses of data from all randomized patients who received at least one dose of study medication and at least one postbaseline assessment were performed. The endpoint for each patient was defined as the last available evaluation. All between-group comparisons were based on 2-tailed tests. Between-group differences in response rates, Clinical Global Impressions change scores, Physical Self-Maintenance Scale items, and Functional Assessment Staging ratings were analyzed using Cochran-Mantel-Haenszel tests adjusted for site. For continuous efficacy measures, changes from baseline were analyzed using analysis of covariance, including treatment, site, baseline score, and treatment by baseline interactions. Pairwise between-treatment p values were calculated using the Fisher least significant difference procedures based on the least squares means. The Holm sequentially rejective, Bonferroni-type procedure was used to compensate for multiple testing.[23] Tests for direct versus indirect effects on improvements in psychosis and aggression used analysis of covariance models in which improvement in psychosis (or aggression) at endpoint was the dependent variable and change in aggression (or psychosis) and site were independent factors; residuals were then used as dependent variables in a second model that included treatment as the independent factor.

RESULTS

Patient Characteristics and Disposition

The study was conducted at 40 sites in the United States from July 31, 1995, to March 7, 1997, with 4 to 32 subjects entered per site. Of the 729 patients screened at baseline, 625 were randomly assigned to receive placebo or risperidone at 0.5, 1, or 2 mg/day (Table 1). Reasons for failure to randomize screened patients included refusal and symptoms that were below the threshold for inclusion or those that were too severe. The 12-week course of treatment was completed by 435 patients (70%), with discontinuations primarily due to adverse events (in 12% of the placebo patients and in 8%, 16%, and 24% of patients receiving 0.5, 1, and 2 mg/day of risperidone, respectively). The proportions of patients who discontinued prematurely ranged from 27% in the placebo group to 42% in the group receiving 2 mg/day of risperidone (see Table 1).

The patients' mean ± SD baseline Mini-Mental State Examination score was 6.6 ± 6.3 (range, 0–23); 96% were at Functional Assessment Staging stage 6A or higher, and 47% were at stage 7A or higher, indicating severe dementia. Severity of psychopathology (Clinical Global Impressions scores) was moderate to marked in 72% of patients and severe in 8%. Previous neuroleptic treatment had been received by 82%. Approximately 9% received antiparkinsonian medication during the study (8% of placebo patients and 7%, 6%, and 13% of patients receiving 0.5, 1, and 2 mg/day of risperidone, respectively), and 32% received lorazepam for agitation during the first 4 weeks (33% of placebo patients and 28%, 32%, and 32% of patients receiving 0.5, 1, and 2 mg/day of risperidone, respectively). The only significant ($p = .02$) difference between treatment groups at baseline was on the Mini-Mental State Examination: mean scores were higher in patients receiving 2 mg/day of risperidone (mean score = 7.97) than placebo (mean score = 6.06). Analysis of covariance indicated that differences between treatment groups remained significant after controlling for baseline Mini-Mental State Examination scores.

Efficacy

Categorical responses defined by a 50% or more reduction in BEHAVE-AD total scores occurred in more patients receiving 1 mg/day (45%; $p = .02$) and 2 mg/day (50%; $p = .002$) of risperidone than placebo (33%).

Patients receiving 1 or 2 mg/day of risperidone improved more than placebo patients on the BEHAVE-AD total score and the psychosis and aggressiveness subscales (Table 2), with significant improvements as early as week 2 (Figure 2). Significant improvements were seen on all of the paranoid/delusional ideation items of the psychosis subscale. Ratings of hallucinations were low (approximately 1.2) at baseline in all groups, with no significant differences between groups in change scores. All 3 risperidone groups had significantly better scores than did placebo patients on the BEHAVE-AD aggressiveness subscale at week 12; risperidone at 1 and 2 mg/day was superior to placebo at endpoint. Significant improvements over time were noted in all 3 risperidone groups on each of

Table 1. Patient Background Characteristics and Disposition[a]

Characteristic	Placebo (N = 163)	Risperidone Dose 0.5 mg/d (N = 149)	Risperidone Dose 1 mg/d (N = 148)	Risperidone Dose 2 mg/d (N = 165)	Total (N = 625)
Men/women, N	53/110	41/108	50/98	57/108	201/424
White/multiracial, N	147/16	133/16	127/21	147/18	554/71
Age, y (mean ± SD)	82.6 ± 7.7	83.2 ± 7.9	83.1 ± 7.2	82.0 ± 7.8	82.7 ± 7.7
Dementia diagnosis, N (%)					
Alzheimer's	115 (70.6)	120 (80.5)	110 (74.3)	111 (67.3)	456 (73.0)
Vascular	27 (16.6)	17 (11.4)	26 (17.6)	27 (16.4)	97 (15.5)
Mixed	21 (12.9)	12 (8.1)	12 (8.1)	27 (16.4)	72 (11.5)
Duration of current stay, mo (mean ± SD)	20.6 ± 23.9	20.4 ± 21.9	22.8 ± 25.0	21.7 ± 22.0	21.4 ± 23.2
MMSE score (mean ± SD)	6.1 ± 5.7	6.2 ± 6.3	6.5 ± 6.4	7.7 ± 6.7	6.6 ± 6.3
FAST stage, N (%)					
≥ 6A	156 (95.7)	143 (96.0)	145 (98.0)	158 (95.8)	602 (96.3)
≥ 7A	80 (49.1)	67 (45.0)	67 (45.3)	78 (47.3)	292 (46.7)
Completed study, N (%)	119 (73.0)	117 (78.5)	103 (69.6)	96 (58.2)	435 (69.6)
Prematurely discontinued, N (%)	44 (27.0)	32 (21.5)	45 (30.4)	69 (41.8)	190 (30.4)
Reason for discontinuation, N (%)					
Adverse event	20 (12.3)	12 (8.1)	24 (16.2)	40 (24.2)	96 (15.4)
Inadequate response	9 (5.5)	9 (6.0)	4 (2.7)	9 (5.5)	31 (5.0)
Other[b]	15 (9.2)	11 (7.4)	17 (11.5)	20 (12.1)	63 (10.1)

[a]Abbreviations: FAST = Functional Assessment Staging, MMSE = Mini-Mental State Examination.
[b]The "other" reasons for premature discontinuation (which were seen in equal proportions in the 4 treatment groups) included the following: chose to discontinue (31 patients), administrative reason (14 patients), ineligible (3 patients), intercurrent illness (3 patients), abnormal laboratory result (2 patients), poor compliance (1 patient), and "other" (9 patients).

Table 2. Mean ± SE Baseline Scores and Changes in BEHAVE-AD Total and Subscale Scores at Week 12 and Endpoint[a]

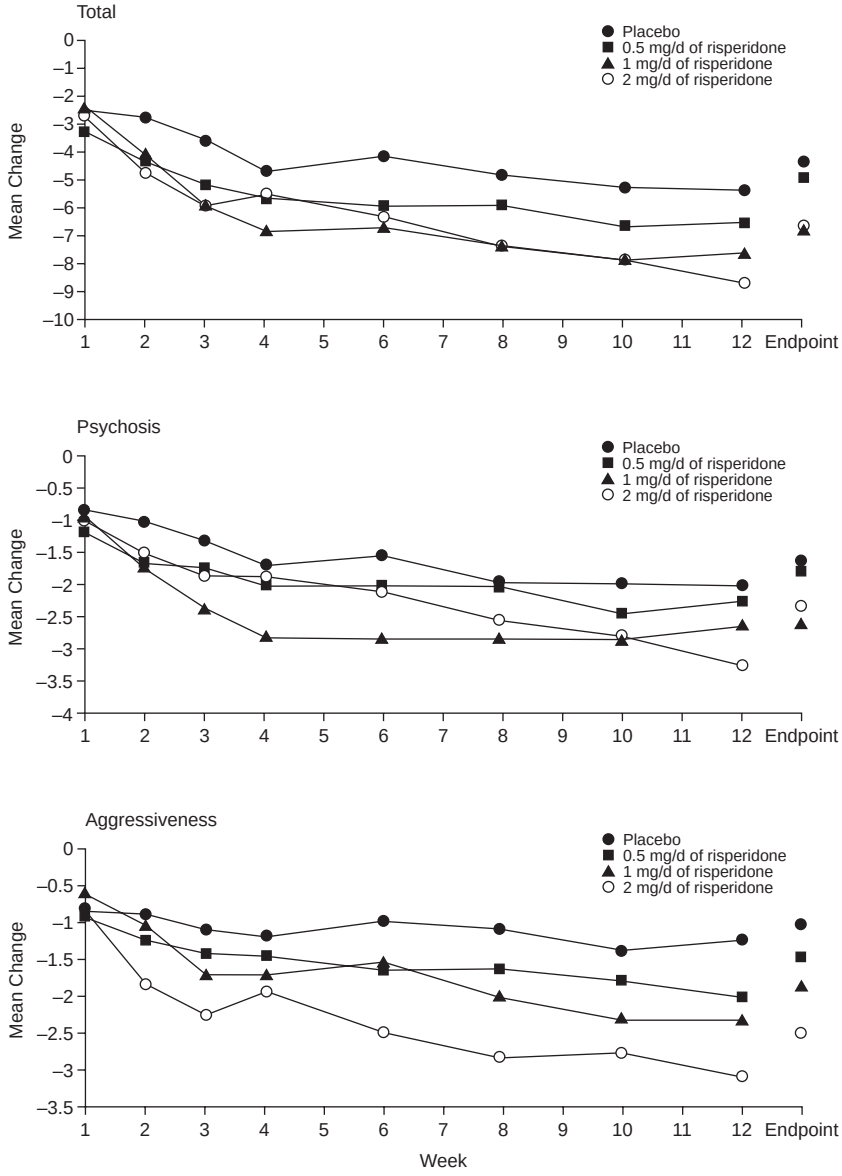
Variable	Placebo	Risperidone Dose 0.5 mg/d	p Value[b]	Risperidone Dose 1 mg/d	p Value[b]	Risperidone Dose 2 mg/d	p Value[b]
N at endpoint	161	146		148		162	
N at wk 12	118	117		102		98	
Total score (range, 0–75)							
Baseline	15.9	15.9		16.0		15.4	
Change at wk 12	–5.2 ± 0.6	–6.4 ± 0.7	.13	–7.4 ± 0.7	.02	–8.5 ± 0.7	< .001
Change at endpoint	–4.2 ± 0.6	–4.8 ± 0.7	.37	–6.5 ± 0.7	.002	–6.4 ± 0.6	.001
Psychosis subscale (range, 0–36)							
Baseline	5.0	5.1		5.1		4.8	
Change at wk 12	–1.9 ± 0.4	–2.2 ± 0.4	.316	–2.6 ± 0.4	.054	–3.2 ± 0.3	.002
Change at endpoint	–1.5 ± 0.3	–1.6 ± 0.3	.68	–2.5 ± 0.3	.005	–2.2 ± 0.3	.01
Aggressiveness subscale (range, 0–9)							
Baseline	4.8	4.8		4.6		5.1	
Change at wk 12	–1.2 ± 0.3	–1.9 ± 0.3	.02	–2.2 ± 0.3	.006	–3.0 ± 0.3	< .001
Change at endpoint	–0.9 ± 0.2	–1.3 ± 0.3	.11	–1.7 ± 0.2	.002	–2.4 ± 0.2	< .001

[a]A lower score indicates less severe symptoms. Abbreviation: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease rating scale.
[b]Versus placebo (Fisher least significant difference procedure based on least squares means from analysis of covariance).

the 3 aggression items. While improvements in the risperidone-treated patients were noted on the other subscales of the BEHAVE-AD (see Appendix 1), the differences versus placebo were not significant.

To determine the effects of risperidone in patients who were overtly violent at baseline, we conducted a post hoc analysis of those with baseline scores of 2 or more on the physical threats or violence item of the aggressiveness subscale (a score of 2 indicates the presence of physical violence, 1 indicates threatening behavior, and 0 indicates no physical threats or violence). In the 193 patients receiving risperidone who were violent at baseline, 125 (65%) were improved (scored 0 or 1 at endpoint) compared with 27 (42%) of the 64 placebo patients (p = .02). Such improvements were seen in 39 (68%) of the 57 patients receiving 1 mg/day of risperidone (p = .06 vs.

Figure 2. Mean Changes From Baseline in BEHAVE-AD Scores[a]



Placebo	159	147	147	141	134	126	124	118	161
0.5 mg/d of risperidone	143	145	139	134	133	123	118	117	146
1 mg/d of risperidone	146	139	127	124	116	110	103	102	148
2 mg/d of risperidone	158	150	140	134	123	109	102	98	162

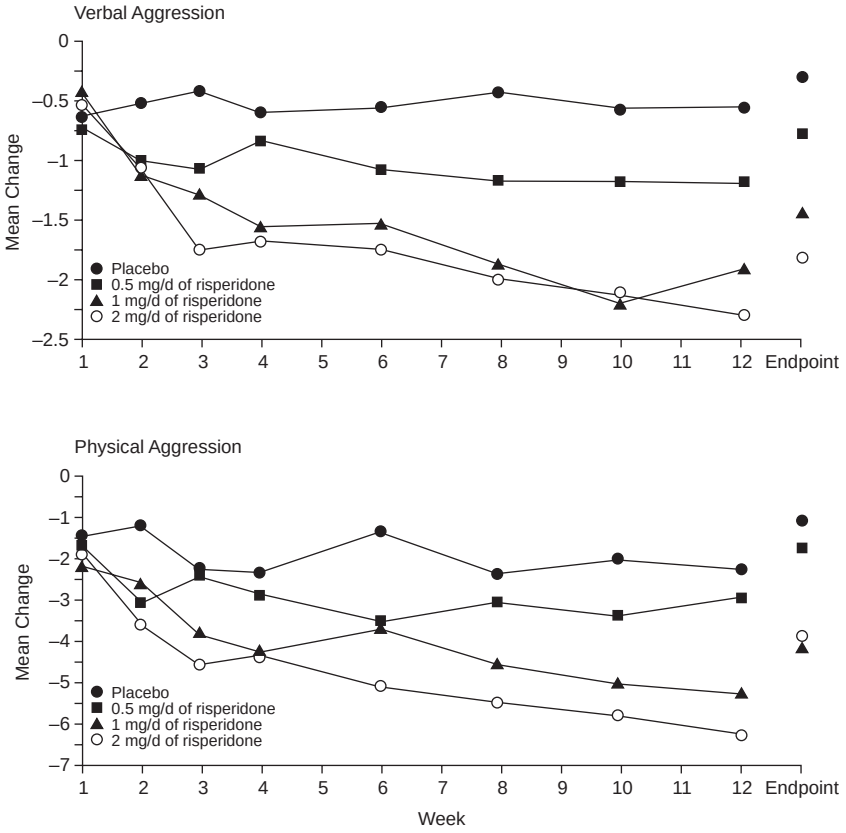
[a]Significant ($p = .05$ to $p < .0001$) differences between placebo and 1 mg/day or 2 mg/day of risperidone were seen as early as weeks 2 or 3 on the total and subscale scores. A lower score indicates less severe symptoms. Below the graphs are the numbers of patients in each treatment group aligned with the week in the graph above.

placebo) and in 52 (71%) of the 73 patients receiving 2 mg/day of risperidone ($p = .02$ vs. placebo).

A direct effect of treatment on aggression was examined in analyses that tested for group differences in aggression after removing the indirect effect resulting from improvements in psychosis (see section on statistical analysis). Risperidone at 1 and 2 mg/day remained superior to placebo on aggression ($p = .01$ and $p \leq .001$, analysis of variance) after controlling for psychosis ($F = 86.3$, $p < .001$). Likewise, 1 mg/day of risperidone (but not 2 mg/day) was superior to placebo ($p = .03$, analysis of variance; $p < .02$, Holm procedure) in having a direct effect on psychosis after controlling for the indirect effect of an improvement in aggression.

Because ratings of the severity of delusional symptoms are based, in part, on the extent to which they lead to an-

Figure 3. Mean Changes From Baseline in Cohen-Mansfield Agitation Inventory Verbal and Physical Aggression Scores[a]



Placebo	161	149	149	143	136	128	126	120	162
0.5 mg/d of risperidone	145	148	142	136	134	125	119	118	149
1 mg/d of risperidone	146	139	129	123	116	110	103	101	147
2 mg/d of risperidone	161	153	143	137	126	111	105	101	163

[a]Significant ($p = .03$ to $p < .001$) differences between placebo and 1 mg/day or 2 mg/day of risperidone were seen as early as weeks 2 or 3. A lower score indicates less frequent symptoms. Below the graphs are the numbers of patients in each treatment group aligned with the week in the graph above.

ger, physical actions, and violence, we also tested for direct effects on delusions by evaluating the proportion of patients with symptoms at baseline, but not at the conclusion of treatment. This change occurred in significantly more patients receiving 1 mg/day or 2 mg/day of risperidone than placebo: in 35 (31%) of 113 patients on placebo, 29 (26%) of 112 patients receiving 0.5 mg/day of risperidone, 49 (45%) of 110 patients receiving 1 mg/day, and 49 (41%) of 120 patients receiving 2 mg/day ($p = .01$ and $p = .05$ for 1 and 2 mg/day vs. placebo, respectively).

Results on the Cohen-Mansfield Agitation Inventory were similar to those described above: patients receiving either 1 or 2 mg/day of risperidone showed significantly greater improvements than did placebo patients at week 12 and endpoint on the verbal, physical, and total aggression scales ($p = .006$ and $p < .001$, analysis of covariance; $p \leq .17$ and $p \leq .025$, Holm procedure), with significant improvements as early as week 2 (Figure 3). These differences reflected significant decreases from baseline in the frequency of each of the physically aggressive behaviors and in 2 of the verbally aggressive behaviors (screaming and cursing) in patients receiving 1 and 2 mg/day of risperidone (but not placebo) ($p = .03$ and $p < .001$ at endpoint; analysis of covariance).

Reductions in mean Clinical Global Impressions scores from baseline to endpoint were greater in those receiving 1 mg/day (from 4.2 to 3.3; $p = .002$, analysis of covariance) or 2 mg/day (from 4.2 to 3.2; $p < .001$) of risperidone than placebo (from 4.2 to 3.7).

There were no significant differences in outcome measures among patients grouped by sex, race, or diagnosis. However, among patients receiving 1 or 2 mg/day of risperidone, older patients tended to improve more than younger patients: 98 (56%) of 176 patients younger than 85 years and 96 (72%) of 134 patients aged 85 years or older showed a 30% or more reduction in BEHAVE-AD total scores. This trend was not so evident among patients receiving placebo: 51% and 54% of placebo pa-

Table 3. Patients Reporting Any Adverse Event and Adverse Events Reported by at Least 10% of Patients in Any Treatment Group

	Placebo (N = 163)		Risperidone Dose 0.5 mg/d (N = 149)		1 mg/d (N = 148)		2 mg/d (N = 165)	
Adverse Event[a]	N	%	N	%	N	%	N	%
Any adverse event	138	84.7	125	83.9	121	81.8	146	88.5
Injury[b]	61	37.4	49	32.9	42	28.4	52	31.5
Somnolence	13	8.0	15	10.1	25	16.9	46	27.9
Fall	33	20.2	24	16.1	19	12.8	41	24.8
Extrapyramidal disorder[c]	12	7.4	10	6.7	19	12.8	35	21.2
Urinary tract infection	21	12.9	24	16.1	19	12.8	35	21.2
Peripheral edema	9	5.5	24	16.1	19	12.8	30	18.2
Purpura	19	11.7	25	16.8	18	12.2	17	10.3
Fever	12	7.4	15	10.1	11	7.4	24	14.5
Pain	13	8.0	12	8.1	4	2.7	17	10.3
Coughing	13	8.0	16	10.7	8	5.4	14	8.5
Agitation	17	10.4	11	7.4	8	5.4	14	8.5
Rhinitis	9	5.5	7	4.7	9	6.1	17	10.3
Upper respiratory tract infection	6	3.7	15	10.1	11	7.4	9	5.5

[a]World Health Organization preferred terms.
[b]Includes accident, diagnostic procedure, hospitalization not otherwise specified, surgical procedure, and injury (World Health Organization adverse event dictionary).
[c]Includes hyperkinesia, hypertonia, tremor, dystonia, involuntary muscle contractions, abnormal gait, hypokinesia, oculogyric crisis, ataxia, hyporeflexia, choreoathetosis, aggravated parkinsonism, and tongue paralysis.

tients in the 2 age groups showed a 30% or more score reduction.

Patients Without Somnolence or Extrapyramidal Symptoms

Because there were dose-dependent increases in somnolence and extrapyramidal symptoms (Table 3), the question arose whether these symptoms could have affected the results. To answer this question, we reanalyzed outcomes in patients who did not experience these symptoms. In patients without somnolence (N = 526) or extrapyramidal symptoms (N = 549), greater reductions were still seen in patients receiving 1 and 2 mg/day of risperidone than in placebo patients on the total and psychosis and aggressiveness subscale scores of the BEHAVE-AD ($p = .023$ and $p = .005$ at endpoint; analysis of covariance). Findings involving Cohen-Mansfield Agitation Inventory scores were similar. Thus, the effects of risperidone on target symptoms cannot be attributed to indirect effects related to somnolence or extrapyramidal symptoms.

Safety and Tolerability

Mean changes in Mini-Mental State Examination scores were –0.20 and –0.74 at week 12 and endpoint, respectively, for patients taking 1 mg/day of risperidone, and –0.14 and –0.64 for those taking 2 mg/day. The change scores were –0.16 and –0.47 at 1 mg/day at week 12 and endpoint, respectively, and 0.31 and –0.28 at 2 mg/day in patients without somnolence or extrapyramidal symptoms; these changes were not significantly different from those with placebo. There were no significant differences between treatment groups on changes in Physical Self-Maintenance Scale total scores or individual items at any visit.

The severity of parkinsonism and hypokinesia (Extrapyramidal Symptom Rating Scale scores) did not differ significantly between patients receiving 0.5 or 1 mg/day of risperidone and placebo patients. However, differences between 2 mg/day of risperidone and placebo were significant: on the parkinsonism total and hypokinesia scales, the changes from baseline to endpoint were –0.22 and 0.17 in placebo patients, –0.48 and 0.01 in patients treated with 0.5 mg/day of risperidone, 0.84 and 0.95 with 1 mg/day of risperidone, and 2.37 and 2.01 with 2 mg/day of risperidone (on both scales, $p < .001$, analysis of covariance). Tardive dyskinesia emerged in 1 patient receiving placebo and in none of the 462 patients exposed to risperidone.

Underscoring the difficulty of discerning true drug effects from intercurrent events, we noted that almost all patients in all 4 treatment groups experienced adverse events: 85% of the placebo group and 84%, 82%, and 88% of patients receiving 0.5, 1, and 2 mg/day of risperidone, respectively (see Table 3). There were, however, dose-related increases in specific adverse effects, including somnolence, extrapyramidal symptoms, and peripheral edema. The mechanism associated with peripheral edema is obscure; all occurrences were mild. No consistent, clinically significant changes in laboratory measures or vital signs occurred during the study. Electrocardiogram values were similar across treatment groups. Ninety patients (21 taking placebo and 16, 24, and 29 taking 0.5, 1, and 2 mg/day of risperidone, respectively) experienced one or more serious adverse events during the trial or the subsequent 30 days; almost all were considered unrelated to medication by investigators. Thirty patients died during the trial or in the subsequent 30 days: 5 in the placebo group and 6, 13, and 6 in patients receiving 0.5, 1, and 2 mg/day of risperidone (not significant). Deaths did not cluster with respect to cause; in all but 3 cases, investigators judged that the deaths resulted from intercurrent illnesses unrelated to study medication. In the 3 cases that were considered to be at least possibly drug related, the serious associated adverse events were pneumonia in one case (at 0.5 mg/day of risperidone), dehydration and abnormal renal function in another (at 1 mg/day), and respiratory insufficiency and pulmonary embolism in the third (at 2 mg/day).

DISCUSSION

Risperidone at doses of 1 or 2 mg/day was significantly more effective than placebo in reducing noncognitive psychiatric and behavioral symptoms in long-term care resi-

dents with dementia. Although risperidone was initially developed to treat schizophrenia, it has significant effects on psychotic symptoms and aggression in patients with dementia. In our study, its effects on these 2 domains of symptoms appear to be independent of each other. Moreover, treatment with risperidone did not cause significant decrements in cognitive performance or self-care. Within the context of nursing home reform, risperidone is acting as a psychotherapeutic agent rather than as a chemical restraint. Risperidone at both 1 and 2 mg/day was shown to be efficacious; some adverse events, however, were more frequent in patients receiving the higher dose. Thus the optimal dose, in terms of both efficacy and safety, for elderly patients with dementia would appear to be 1 mg/day.

The heterogeneity of the patient population with respect to their causes of dementia and subject selection based primarily on overall behavioral pathology may limit the extent to which one can draw pathophysiologic conclusions from the study findings. However, it mirrors the public health context and the "real world" clinical problems of caring for elderly patients with dementing illnesses. The patients treated in this trial suffered, on average, from rather severe dementia, with a mean Mini-Mental State Examination score of 6.6 at baseline. They are likely to be representative of the population of nursing home residents who require treatment for symptoms of psychosis, aggression, and agitation. The antipsychotic effects of risperidone in patients with advanced dementia are similar to those in more intact elderly patients with psychotic disorders,[24] suggesting that risperidone would also be of value in patients with milder Alzheimer's disease and related disorders.

The results reported here were based primarily on endpoint analyses that included the 95% of subjects for whom at least one evaluation was conducted after randomization. Confidence in these findings is supported by their similarity to those for the 70% of subjects who completed the full 12 weeks of double-blind treatment. Risperidone, particularly at 1 mg/day, was well tolerated even in an old and frail study sample, independent of whether patients experienced sedation or extrapyramidal symptoms. As a measure of its relative safety, total rates of treatment discontinuation and termination owing to adverse events were similar in patients receiving placebo and risperidone doses up to 1 mg/day. These rates also suggest that it may, at times, be difficult to distinguish between adverse events of risperidone and spontaneously occurring adverse events.

According to both family caregivers and nursing home personnel, aggression is the most serious noncognitive symptom seen in patients with dementia. Aggressive behavior is a common precipitant of nursing home admission, and violence is a constant clinical problem in the nursing home. Substantial improvements in aggressive behavior were seen with risperidone in the present study: reductions in both the severity and frequency of aggression were twice as great or even greater in patients receiving 1 and 2 mg/day of risperidone than in the placebo group. Results of the subanalysis of patients who demonstrated overtly violent behavior at baseline showed that almost 70% of these patients who were given risperidone (1 or 2 mg/day) changed from displaying physical violence to not being physically aggressive. Further evidence for clinical significance comes from patient responses to the Clinical Global Impressions scale, a measure of general psychopathology: in patients receiving 1 or 2 mg/day of risperidone, scores improved from moderate severity to mild symptomatology (roughly from scores of 4 to 3), while patients on placebo remained in the moderate range.

Our results indicate that risperidone is efficacious and safe for the treatment of psychotic and aggressive symptoms in patients with Alzheimer's disease and vascular dementia. Atypical antipsychotic medications such as risperidone have significantly changed the treatment of schizophrenia, and the data presented here suggest that risperidone can also improve the care of demented patients with delusions and behavioral symptoms. Although risperidone appears to have a favorable risk-benefit profile, it is still important to evaluate patients with relevant symptoms before initiating treatment with an antipsychotic agent.[10] When such treatment is necessary, it can be implemented with relative safety with risperidone at a dose of 1 mg/day. Since psychotic and behavioral symptoms frequently begin before nursing home placement, these findings may apply to patients with similar problems who remain in the community.

Drug names: benztropine (Cogentin and others), chloral hydrate (Noctec), lorazepam (Ativan and others), risperidone (Risperdal).

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Appendix 1. Items of the 7 Major Categories of the Behavior Pathology in Alzheimer's Disease Rating Scale and of the Aggressive Subscales of the Cohen-Mansfield Agitation Inventory

Behavioral Pathology in Alzheimer's Disease rating scale
- Paranoid and delusional ideation
  - "People are stealing things" delusion
  - "One's house is not one's home" delusion
  - "Caregiver (or nurse or nursing aide) is an imposter" delusion
  - Delusion of abandonment
  - Delusion of infidelity
  - Suspiciousness or paranoia (other than above)
  - Delusions (other than above)
- Hallucinations
  - Visual
  - Auditory
  - Olfactory
  - Haptic (sense of touch)
  - Other
- Activity disturbances
  - Wandering: away from home
  - Purposeless activity
  - Inappropriate activity
- Aggressiveness
  - Verbal outbursts
  - Physical threats or violence
  - Agitation (other than above)
- Diurnal rhythm disturbances
  - Day/night disturbance
- Affective disturbance
  - Tearfulness
  - Depressed mood: other
- Anxieties and phobias
  - Anxiety regarding upcoming events
  - Other anxieties
  - Fear of being left alone
  - Other phobias

Cohen-Mansfield Agitation Inventory
- Physically aggressive behaviors
  - Hitting
  - Kicking
  - Grabbing people
  - Pushing
  - Throwing things
  - Biting
  - Scratching
  - Spitting
  - Hurting self or others
  - Tearing things or destroying property
  - Making physical sexual advances
- Verbally aggressive behaviors
  - Screaming
  - Making verbal sexual advances
  - Cursing or verbal aggression