A Randomized Placebo-Controlled Trial of Risperidone for the Treatment of Aggression, Agitation, and Psychosis of Dementia

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Background: This randomized, double-blind, placebo-controlled trial examined the efficacy and safety of risperidone in the treatment of aggression, agitation, and psychosis in elderly nursing-home patients with dementia.

Method: Elderly patients with a DSM-IV diagnosis of dementia of the Alzheimer's type, vascular dementia, or a combination of the 2 (i.e., mixed dementia) and significant aggressive behaviors were randomized to receive, for a period of 12 weeks, a flexible dose of either placebo or risperidone solution up to a maximum of 2 mg/day. Outcome measures were the Cohen-Mansfield Agitation Inventory (CMAI), the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale, and the Clinical Global Impression of Severity (CGI-S) and of Change (CGI-C) scales.

Results: A total of 345 patients were randomized to treatment with risperidone or placebo, and 337 patients received at least one dose of study drug. The trial was completed by 67% of patients in the placebo group and 73% of patients in the risperidone group. The mean ± SE dose of risperidone was 0.95 ± 0.03 mg/day. The primary endpoint of the study, the difference from baseline to endpoint in CMAI total aggression score, showed a significant reduction in aggressive behavior for risperidone versus placebo ($p < .001$). A similar improvement was also seen for the CMAI total non-aggression subscale ($p < .002$) and for the BEHAVE-AD total ($p < .001$) and psychotic symptoms subscale ($p = .004$). At endpoint, the CGI-S and the CGI-C scores indicated a significantly greater improvement with risperidone compared with placebo ($p < .001$). Overall, 94% and 92% of the risperidone and placebo groups, respectively, reported at least 1 adverse event. Somnolence and urinary tract infection were more common with risperidone treatment, whereas agitation was more common with placebo. There was no significant difference in the number of patients who reported extrapyramidal symptoms between the risperidone (23%) and placebo (16%) groups.

Conclusion: Treatment with low-dose (mean = 0.95 mg/day) risperidone resulted in significant improvement in aggression, agitation, and psychosis associated with dementia.

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The number of people with dementia is expected to increase with the aging world population. It has been estimated that the prevalence of dementia doubles every 5 years after the age of 65 years,[1,2] with Alzheimer's disease (AD) and vascular dementia accounting for most cases of dementia (67% and 15%, respectively).[3] Agitation, aggression, and psychosis (delusions and hallucinations) complicate dementia in 60% to 90% of cases,[1,4–6] with most symptoms appearing in the later stages.[7] The prevalence of these symptoms is particularly high in nursing-home residents. A previous study in Australia indicated that over 90% of residents exhibit at least 1 behavioral symptom, most notably aggression (76.5%).[8] Another study reported that 29% of residents displayed at least 1 problem behavior for much of the time.[9]

Agitation, and aggression specifically, is considered the most serious noncognitive symptom experienced in patients with dementia in that it causes much distress to family and caregivers as well as the patient. These symptoms often underlie the decision to institutionalize a patient.[10] This necessitates the development of effective management strategies, the use of psychological and environmental strategies,[11,12] and judicious prescribing of psychotropics.

Antipsychotic medications have long been used for the treatment of aggression, agitation, and psychosis in patients with dementia. Conventional antipsychotics have had modest effects in the treatment of these symptoms, with 1 meta-analysis concluding that only 18% of dementia patients benefited from neuroleptic treatment beyond that of placebo.[13] In addition, their use has been limited due to an undesirable side effect profile to which the elderly population is particularly sensitive. These side effects include sedation, orthostatic hypotension, anticholinergic symptoms, and the development of abnormal involuntary movements, including tardive dyskinesia.[14] Risperidone, an atypical antipsychotic, is associated with significantly fewer adverse events than conventional antipsychotics, particularly, extrapyramidal symptoms (EPS). In addition, risperidone lacks anticholinergic properties and thus may be especially useful in treating the elderly with dementia complicated by aggression, agitation, or psychosis.[15–17]

Two recent trials of risperidone in the treatment of institutionalized elderly patients with dementia complicated by behavioral disturbances concluded that risperidone significantly improved symptoms of aggression.[18,19] The EPS profile of risperidone (at a dose of 1 mg/day) was similar to that of placebo,[18,19] while risperidone induced fewer EPS than haloperidol at clinically effective doses.[18]

As the benefits of risperidone in the 2 previous studies were particularly notable on measures of aggressive behavior, this study set out to investigate the effects of risperidone in nursing-home residents exhibiting this behavior in particular. The current study thus enrolled patients with a minimum score for aggressive behavior rather than general behavioral or psychological disturbances. Furthermore, in contrast to a previous study,[19] the dose regimen in this study was flexible.

The purpose of this study was to evaluate the efficacy, safety, and tolerability of risperidone versus placebo in treating aggression primarily, as well as agitation and psychosis, in nursing-home patients with AD, vascular dementia, or mixed dementia.

METHOD

Patient Selection

Inclusion criteria were a diagnosis of dementia with aggressive behaviors; dementia was of the Alzheimer's type, vascular dementia, or a combination of the 2 (i.e., mixed dementia), according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[20] Patients were required to be ≥ 55 years of age and to have a score of ≥ 4 on the Functional Assessment Staging Test (FAST)[21] and ≤ 23 on the Mini-Mental State Examination (MMSE).[22] Eligible patients were required to have at least a minimum aggression score on the Cohen-Mansfield Agitation Inventory (CMAI)[23]: a score of ≥ 4 on at least 1 aggressive item, or a score of 3 on at least 2 aggressive items, or a score of 2 on at least 3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3. Patients had to reside in a nursing home for at least 1 month prior to enrollment. Caregivers of these patients were professionally trained nurses who could assist with medication and who could assess patient functioning.

Exclusion criteria included medical or neurologic conditions other than dementia that diminish cognitive function, other types of dementia, major depression within the last 6 months, other psychiatric disorders that could have accounted for observed psychotic disturbances, a history of tardive dyskinesia, clinically uncontrolled organic disease, clinically relevant laboratory abnormalities, administration of a depot neuroleptic within 2 treatment cycles, a history of neuroleptic malignant syndrome or an allergic reaction to neuroleptic drugs, history of failure to respond to risperidone treatment of at least 4 weeks' duration, and participation in clinical trial(s) with any investigational drugs during the 4 weeks preceding selection. All patients prematurely discontinuing the trial were seen for a final evaluation.

The trial was performed in accordance with the Declaration of Helsinki. Institutional review board approval was obtained at each trial center, and for all patients, a member of their family or legal guardian gave written informed consent after the procedure and possible side effects were fully explained. Guardianship Board approval was obtained in those states in Australia where required by law.

Trial Design

This was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week trial conducted between February 19, 1998, and February 7, 2001, at 14 sites in Australia and New Zealand.

Eligible patients were randomly assigned to 1 of 2 treatment groups (risperidone or placebo) according to a randomization code that was balanced to ensure even distribution of patients in each treatment group at each center. The double-blind treatment period was preceded by a maximum 7-day, single-blind washout period, during which patients took 0.5 mL of placebo oral solution each evening while existing psychotropic medication was discontinued. Short-acting benzodiazepines were allowed for the treatment of insomnia, provided the dosage had been stable for at least 3 months. If a patient's behavioral problems significantly worsened, the double-blind phase of the trial was commenced immediately. Under such circumstances, the existing neuroleptic treatment was tapered to allow cessation of treatment by baseline.

During the double-blind treatment period, trial medication consisted of either risperidone, 1 mg/mL, or placebo solution. Patients started the double-blind phase with 0.25 mL b.i.d. In case of insufficient response, the dosage was

adjusted by increments of 0.25 mL b.i.d., no faster than every other day. Dosing was flexible throughout the treatment period according to patient response and investigator judgment. The maximum allowable dose of risperidone or placebo was 2 mL daily, corresponding to 2 mg of risperidone in the risperidone treatment group.

Concomitant use of antipsychotics, antidepressants, or mood stabilizers or initiation of long-acting benzodiazepines was not permitted during the study, but certain treatments were allowed, provided that the dosage had been stable for at least 3 months prior to the study, to prevent an influence on study outcome. Anticholinergic medication was allowed to treat EPS only if a reduction in trial medication dose was not effective. Treatment of urinary incontinence with low-dose tricyclic antidepressants or anticholinergic medication was allowed to continue. Low-dose oxazepam was permitted to treat agitation, provided that usage did not exceed 4 days in a 7-day period. Short-acting sedative/hypnotic agents prescribed chronically for insomnia at baseline were permitted if the clinician judged that they could not be discontinued. Under exceptional circumstances, initiation of night sedation for insomnia was allowed using a short-acting benzodiazepine (preferably oxazepam at the lowest effective dose). Medication for other disorders (such as hypertension and diabetes) was kept as constant as possible during the trial period. Narcotic analgesics were permitted, provided that the dosage had been stable for at least 3 months and that they were not prescribed to control agitation or aggression.

Assessments

Efficacy parameters were scored on the CMAI,[23] the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale,[24] the Clinical Global Impression of Severity (CGI-S) scale, and the Clinical Global Impression of Change (CGI-C) scale.[25] Nurses responsible for daily care of patients were interviewed by an experienced and trained research nurse who subsequently rated the scales. There was no change in research nurse during the course of the study, and, where possible, visits were timed to coincide with the duty days of the same caregivers.

The primary efficacy outcome was the CMAI total aggression score. Secondary efficacy outcomes were the CMAI total non-aggression score; individual CMAI subscale scores; the BEHAVE-AD total score, psychotic symptom subtotal, and global rating scores; and the CGI-S and CGI-C scores. The CMAI and BEHAVE-AD were evaluated at selection and baseline, at weeks 4 and 8, and at endpoint, which was either week 12 or the patient's last visit. The 29-item CMAI provides a physical (e.g., hitting) and verbal (e.g., screaming) aggression scale, the scores of which can be combined to give a total aggression subscale score (range, 14–98). The CMAI also provides a physical (e.g., wandering) and verbal (e.g., grunting) non-aggression scale, the scores of which can be combined to give a total non-aggression subscale score (range, 15–105).[23] The 25-item BEHAVE-AD provides 7 subscales: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias.[24] The sum of these subscales provides the BEHAVE-AD total score (range, 0–75). The psychosis subscale (range, 0–36) is the sum of the paranoid and delusional ideation and hallucinations subscales. The BEHAVE-AD global rating score was based on a 4-point scale of increasing severity: not (0), mildly (1), moderately (2), and severely (3) disturbing or dangerous to patient or environment.

The CGI-S and the CGI-C were evaluated at selection; at baseline; at weeks 1, 2, 3, 4, and 8; and at endpoint (week 12 or last visit) by specifically trained raters, as well as by the patients' primary caregivers. The CGI-S scale is a 7-point scale ranging from 1 = normal to 7 = extremely severe.[25] The CGI-C is a 7-point scale ranging from 1 = much better, through 4 = neither better nor worse, to 7 = much worse.[25] Finally, FAST[21] and MMSE[22] were assessed at selection and at week 12 (or last visit).

Safety evaluation included monitoring the presence and severity of EPS at each visit and ratings on the Extrapyramidal Symptom Rating Scale (ESRS).[26] Full medical and neurologic examinations and standard laboratory testing were performed at screening and at endpoint. In addition, adverse events were documented throughout the trial period.

Analyses

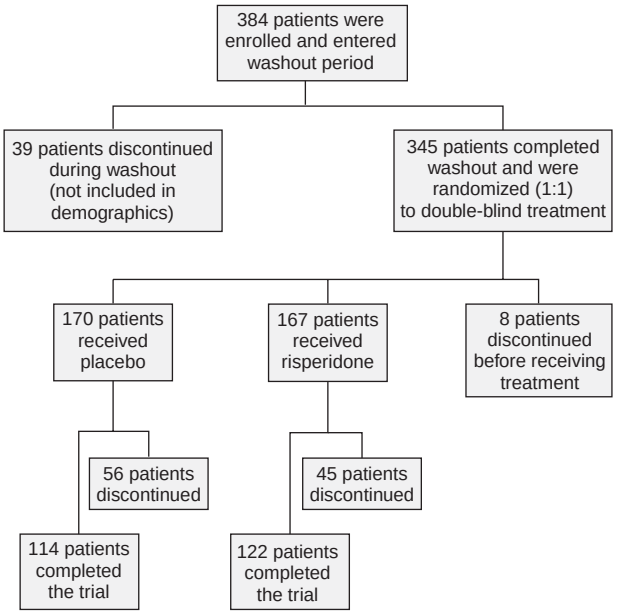
All efficacy analyses were based on an intent-to-treat population. Questions about adherence to documentation procedures (though not about trial or patient care procedures) led to the exclusion of 1 site with 32 patients who were subsequently excluded from the efficacy analyses, but who were included in the safety analysis.

Efficacy. Efficacy was measured as the shift from baseline to endpoint for CMAI, BEHAVE-AD, and CGI scores. The shift for the MMSE and FAST scores was calculated relative to screening, because they were not measured at baseline.

To determine whether the effect of risperidone on aggression was related to an antipsychotic effect or to somnolence, a subanalysis was done for CMAI total aggression scores in patients with and without psychosis at baseline and in patients without somnolence (i.e., no somnolence as an adverse event). Patients were rated as psychotic at baseline if they had a score of ≥ 2 on any BEHAVE-AD delusion or hallucination item.

Safety. All patients who took double-blind medication were included in the analysis of the following safety data: adverse events, EPS-related adverse events, clinical laboratory tests, ESRS scores, and vital signs (blood pressure, heart rate, and body weight). All adverse events were rated as "mild," "moderate," or "severe" by the investigators.

Figure 1. Trial Profile of the Flow of Patients From Recruitment Through Study Completion



Serious adverse events were defined as life-threatening, requiring hospitalization, or resulting in significant disability or incapacity. The use of anti-EPS medications and the occurrence of deaths were monitored.

Regarding ESRS scores, the change from baseline to the maximum severity during double-blind treatment was calculated for the following clusters: total questionnaire, parkinsonism, dyskinesia, dystonia, CGI severity of parkinsonism, CGI severity of dyskinesia, and total ESRS (parkinsonism + dyskinesia + dystonia).

Statistical Analysis

On the assumption that a difference of 4.15 points on the CMAI total aggression score between risperidone and placebo is clinically relevant, it was calculated that 218 patients (109 per treatment group) were required to detect this difference at a 5% significance level with 80% power. Assuming that 30% of the patients would discontinue prematurely, it was calculated that 155 patients per treatment group were to be recruited.

Treatment groups were compared for the CMAI, BEHAVE-AD, and ESRS subtotals using a t statistic derived from an ANCOVA model controlling for treatment, investigator, and baseline values at each assessment and at endpoint. Further analyses were also planned on the last observation carried forward at weeks 4 and 8. To determine if the treatment effect was homogeneous among sites, a site-by-treatment interaction was analyzed using an F test derived from an ANCOVA model controlling for treatment, investigator, baseline value, and the interaction of treatment and investigator. Treatment differences in CGI-C and in the shift from baseline of the CGI-S, MMSE, FAST, and BEHAVE-AD global rating scales scores were compared using a chi-square statistic derived from a Van Elteren test controlling for investigator. A repeated-measures analysis was also performed for the CMAI total aggression scale and the psychotic subscale.

The number of patients requiring anti-EPS medication or benzodiazepines during double-blind treatment was compared by means of a chi-square statistic derived from a Cochran-Mantel-Haenszel test for general association controlling for center. The time to first re-administration of anti-EPS medication was estimated using the Kaplan-Meier product-limit method, and treatment groups were compared via a chi-square statistic derived from a generalized Wilcoxon test. Within-group comparisons of blood pressure, body mass index, and weight were made via paired t tests, and between-group comparisons were made via an ANCOVA model with factors for treatment and investigator and baseline values as covariates. All statistical tests were interpreted at a 5% significance level (2-tailed).

RESULTS

The efficacy measurements were analyzed with the exclusion of 1 site (with 32 patients), which did not adhere to documentation procedures. A repeat of all analyses with the 32 patients from that site included indicated no differences in results.

As depicted in Figure 1, 384 patients were enrolled, of whom 39 dropped out during the washout period. A total of 26 patients dropped out because of ineligibility to continue the trial, 1 patient withdrew consent, and 12 patients dropped out for other reasons. These patients did not receive double-blind treatment and were not included in the demography, efficacy, or safety analyses.

Of the remaining 345 patients, 172 were assigned to placebo treatment and 173 to risperidone treatment. Before receiving treatment, 2 randomized patients died, 5 were withdrawn from the study because of adverse events, and 1 patient withdrew consent. Thus, 170 patients in the placebo group and 167 patients in the risperidone group received at least 1 dose of study drug.

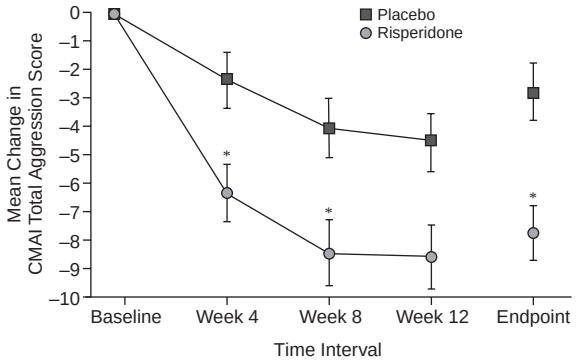
In the placebo group, 114 patients (67.1%) completed the trial, while 56 (32.9%) did not complete the trial. In the risperidone group, 122 patients (73.1%) completed the trial, and 45 (26.9%) did not. The most common reasons for discontinuation were insufficient response (19.4% for the placebo group, 9.6% for the risperidone group) and adverse events (8.2% for the placebo group, 13.2% for the risperidone group). Minor protocol deviations, mainly treatment deviation, intercurrent disallowed medication, and investigator error (e.g., assessments made outside the visits scheduled as specified in the

Table 1. Baseline Characteristics of Patients at Included Sites

Characteristic	Placebo (N = 156)	Risperidone (N = 153)
Female, N (%)	113 (72.4)	109 (71.2)
Age in years, mean (SE)	82.7 (0.64)	83.2 (0.51)
> 74 y, N (%)	134 (85.9)	138 (90.2)
Weight in kilograms, mean (SE)	55.88 (1.14)	55.93 (1.03)
Diagnosis, N (%)		
Alzheimer's dementia	93 (59.6)	87 (56.9)
Vascular dementia	44 (28.2)	44 (28.8)
Mixed dementia	19 (12.2)	22 (14.4)
MMSE score, mean (SE)[a]	5.78 (0.46)	5.14 (0.45)
FAST score, median (min–max)[a]	10.0 (4–16)	10.0 (5–14)
Years since onset of dementia (SE)	5.4 (0.34)	5.3 (0.32)
Years to onset of behavioral disturbance (SE)	3.0 (0.24)	3.1 (0.27)
CMAI total aggression (SE)	33.0 (0.99)	34.1 (1.05)
BEHAVE-AD total score (SE)	18.6 (0.87)	19.0 (0.90)

[a]Measured at screening (placebo: N = 147, risperidone: N = 146).
Abbreviations: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease, CMAI = Cohen-Mansfield Agitation Inventory, FAST = Functional Assessment Staging Test, MMSE = Mini-Mental State Examination.

Figure 2. Change (mean and SE) in Total Aggression Subscale Score of the CMAI Over Time (intent-to-treat patients at included sites)



*p < .01 vs. placebo.
Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.

protocol), were noted in 118 patients, 65 in the placebo group (38.2%) and 53 in the risperidone group (31.7%).

Demographic and Other Baseline Characteristics

Demographic and baseline clinical and outcome data were very similar for the risperidone and placebo groups (Table 1). Patients had a wide range of concomitant diseases, none of which was thought to influence the course of the trial. There were no statistically significant differences between the groups in the frequency of these conditions. In addition, little variation was observed between the 2 groups in the number of patients who received previous neuroleptic or other psychotropic medication, nor in the number of patients receiving concomitant treatment.

Drug Dose and Duration

Patients were treated with placebo medication for a mean of 69.3 days (SE = 1.95; range, 5–92) and with risperidone for a mean of 73.0 days (SE = 1.81; range, 3–111). The mean dose of risperidone was 0.95 mg (SE = 0.03), and the mean of the individual modal dose was 0.99 mg (SE = 0.05). The mean placebo dose of 1.06 mL (SE = 0.03) was significantly higher than the mean risperidone dose ($t = 2.443$, $df = 302$, $p = .015$).

Primary Efficacy Outcome

CMAI total aggression subscale. Improvement of aggression, determined by the total aggression subscale score of the CMAI, was observed during the treatment period (Figure 2). Mean changes indicated significantly greater improvement in the risperidone group than in the placebo group ($p < .01$) at all but the week 12 evaluation, where the difference approached statistical significance ($p = .058$).

The least-squares mean (mean adjusted for the effect of baseline score and investigator) of the CMAI total aggression score decreased by 4.4 more in risperidone-treated patients than in placebo-treated patients ($p < .001$) (Table 2). Since the minimum score was 14 and the mean baseline score was 33, this difference of 4.4 represents more than a 23% greater decrease in aggression in the risperidone group.

There was no statistically significant or clinically important interaction between treatment group and investigator, indicating that the treatment effect was homogeneous among the sites.

Evaluation of the repeated-measures analysis demonstrated a significant improvement in CMAI score for risperidone over placebo at weeks 4 through 12 ($p = .0002$), irrespective of the slightly higher dropout rate in the placebo group.

Secondary Efficacy Outcomes

Other CMAI subscales. Except for physical nonaggression ($p = .071$), mean differences for all subscales of the CMAI indicated a significantly ($p < .01$) greater improvement in the risperidone than in the placebo group at endpoint and at most evaluation times during treatment, indicating a positive effect of risperidone on both aggressive and non-aggressive, agitated behaviors.

Treatment effects were consistent across sites; there were no significant interactions between treatment and investigator site for any parameter or at any timepoint. As was the case with the total aggression subscale, there was some evidence of a significant baseline-by-treatment interaction for verbal and physical aggression, indicating that the effect of risperidone relative to placebo increased with the frequency of aggression at baseline.

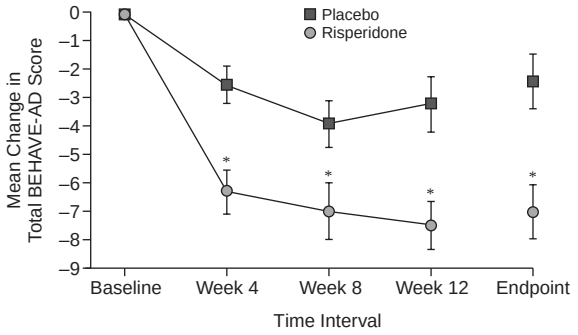
BEHAVE-AD. The least-squares mean scores for changes in the BEHAVE-AD total and psychotic symptoms subtotal showed significantly greater improvement

Table 2. CMAI and BEHAVE-AD Rating Scale Score Change From Baseline for All Intent-To-Treat Patients at Included Sites

Rating Scale	Placebo (N = 152) LS Mean Change From Baseline	Risperidone (N = 149) LS Mean Change From Baseline	Differences in LS Means (95% CI)	p Value[a]
CMAI				
Total aggression	–3.1	–7.5	–4.4 (–6.75 to –2.07)	< .001
Physical aggression	–2.8	–5.4	–2.6 (–4.45 to –0.67)	.008
Verbal aggression	–0.2	–2.1	–1.8 (–2.51 to –1.18)	< .001
Total non-aggression	–2.8	–7.3	–4.5 (–7.39 to –1.70)	.002
Physical non-aggression	–2.5	–4.3	–1.8 (–3.75 to 0.15)	.071
Verbal non-aggression	–0.3	–3.0	–2.8 (–4.16 to –1.37)	< .001
BEHAVE-AD				
Total score	–2.3	–6.8	–4.5 (–6.45 to –2.46)	< .001
Psychotic symptom subtotal	–0.7	–2.0	–1.4 (–2.26 to –0.44)	.004
Paranoid and delusional ideation	–0.7	–1.4	–0.8 (–1.38 to –0.15)	.015
Hallucinations	0.0	–0.6	–0.6 (–1.04 to –0.14)	.010
Activity disturbances	–0.4	–0.8	–0.4 (–0.89 to 0.03)	.067
Aggressiveness	–0.5	–2.0	–1.5 (–2.08 to –0.95)	< .001
Diurnal rhythm disturbances	–0.2	–0.3	–0.2 (–0.34 to 0.03)	.098
Affective disturbance	–0.2	–0.5	–0.3 (–0.57 to –0.02)	.034
Anxiety and phobias	–0.4	–1.1	–0.7 (–1.12 to –0.21)	.004

[a]Test for no difference between treatments from ANCOVA model with factors for treatment and investigator and baseline scores as covariates. Lower scores indicate less psychopathology.
Abbreviations: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease, CI = confidence interval, CMAI = Cohen-Mansfield Agitation Inventory, LS = least-squares.

Figure 3. Change (mean and SE) in BEHAVE-AD Total Score Over Time (intent-to-treat patients at included sites)



	Baseline	Week 4	Week 8	Week 12	Endpoint
Placebo:	N = 153	N = 138	N = 123	N = 112	N = 152
Risperidone:	N = 151	N = 141	N = 132	N = 119	N = 149

*p < .01 vs. placebo.
Abbreviation: BEHAVE-AD = Behavioral Pathology of Alzheimer's Disease.

Table 3. Change From Baseline CGI at Endpoint (intent-to-treat patients at included sites)

Change From Baseline at Endpoint	Placebo (N = 153) N (%)	Risperidone (N = 150) N (%)
Investigator rated[a]		
Very much improved	6 (3.9)	18 (12.0)
Much improved	22 (14.4)	43 (28.7)
Minimally improved	28 (18.3)	34 (22.7)
Unchanged	53 (34.6)	33 (22.0)
Minimally worse	16 (10.5)	11 (7.3)
Much worse	23 (15.0)	8 (5.3)
Very much worse	5 (3.3)	3 (2.0)
Caregiver rated[a]		
Very much improved	7 (4.6)	13 (8.7)
Much improved	23 (15.0)	43 (28.7)
Minimally improved	30 (19.6)	39 (26.0)
Unchanged	42 (27.5)	26 (17.3)
Minimally worse	15 (9.8)	13 (8.7)
Much worse	24 (15.7)	12 (8.0)
Very much worse	12 (7.8)	4 (2.7)

[a]Overall p value < .001; Van Elteren test controlling for investigator.
Abbreviation: CGI = Clinical Global Impression.

in the risperidone group than in the placebo group at endpoint and at most evaluations during treatment (Table 2). This was also observed for the BEHAVE-AD subscales, with the exception of activity disturbances (p = .067) and diurnal rhythm disturbances (p = .098). At endpoint, the median BEHAVE-AD global rating score for the placebo group was 2.0, compared with 1.0 for the risperidone group (p = .003).

Improvement in the BEHAVE-AD total score was observed beginning at week 4 and continuing throughout treatment (Figure 3). Mean changes in the observed mean scores indicated significantly (p < .01) greater improvement in the risperidone group than in the placebo group at all points of evaluation.

The treatment effect did not vary by site. For several parameters, including the BEHAVE-AD total score and the psychotic symptom subtotal, the higher the patient's baseline score, the larger the effect of risperidone relative to placebo.

CGI. At endpoint, the CGI-C as assessed by both the investigator and the caregiver indicated greater (p < .001) improvement for the risperidone group than for the placebo group (Table 3). Statistically significant differences between groups were also observed for CGI-S as assessed

by investigators at weeks 2, 4, 8, 12 and at endpoint ($p < .001$) and as assessed by caregivers at weeks 8, 12 and at endpoint ($p < .01$).

MMSE and FAST

No changes were observed in the mean MMSE or median FAST scores in either group during the trial, indicating that treatment with risperidone did not result in overall cognitive or functional deterioration.

Subanalyses

To assess whether reduced aggression was related to psychotic status, a subanalysis was performed in patients with and without psychosis at baseline. The CMAI total aggression subscale score was significantly reduced at endpoint with risperidone compared with placebo both in patients without psychosis at baseline (N = 72 for risperidone and N = 72 for placebo; $p = .04$) and in those with psychosis (N = 81 for risperidone and N = 79 for placebo; $p = .001$). To assess whether reduced aggression was secondary to sedation, the CMAI total aggression subscale score was analyzed in patients without somnolence reported as an adverse event (N = 87 for risperidone and N = 109 for placebo). Scores for CMAI total aggression at endpoint were still significantly different ($p < .01$) in favor of risperidone in patients without somnolence.

Safety Evaluation

The total number of patients from all sites who reported adverse events during the double-blind treatment period was 157 in both groups (92.4% and 94.0% in the placebo group and risperidone group, respectively). The adverse events reported by ≥ 5% of the patients in either treatment group are summarized in Table 4 using the World Health Organization preferred terms. Injury, somnolence, falls, and urinary tract infections were the most common adverse events, but only somnolence and urinary tract infections were more common in the risperidone group than in the placebo group. A total of 36 patients (21.2%) in the placebo group and 39 patients (23.4%) in the risperidone group had at least 1 adverse event that was rated as "severe" by the investigator. There was no significant difference in the proportions of severe adverse events that were considered related or not related to the study medication in the 2 groups.

Serious Adverse Events

Ten patients, 4 (2.4%) in the placebo group and 6 (3.6%) in the risperidone group, died during the course of the trial. The most frequent causes of death were pneumonia (3 in the risperidone and 1 in the placebo group) and stroke (2 in the risperidone group). In all cases, the investigators considered the adverse events leading to the patients' deaths to have no drug relationship or considered any drug relationship to be doubtful.

Table 4. Adverse Events Reported by at Least 5% of Patients in Either Group at All Sites

Adverse Event[a]	Placebo (N = 170) N (%)	Risperidone (N = 167) N (%)
Somnolence	43 (25.3)	61 (36.5)
Injury	63 (37.1)	60 (35.9)
Fall	46 (27.1)	42 (25.1)
Urinary tract infection	25 (14.7)	39 (23.4)
Agitation	42 (24.7)	33 (19.8)
Purpura	27 (15.9)	30 (18.0)
Conjunctivitis	18 (10.6)	20 (12.0)
Constipation	26 (15.3)	19 (11.4)
Skin disorder	16 (9.4)	18 (10.8)
Cerebrovascular adverse event	3 (1.8)	15 (9.0)
Vomiting	13 (7.6)	14 (8.4)
Edema peripheral	6 (3.5)	13 (7.8)
Rash	9 (5.3)	13 (7.8)
Upper respiratory tract infection	15 (8.8)	13 (7.8)
Skin ulceration	11 (6.5)	12 (7.2)
Extrapyramidal disorder	5 (2.9)	10 (6.0)
Tremor	3 (1.8)	10 (6.0)
Gait abnormal	2 (1.2)	10 (6.0)
Fever	4 (2.4)	9 (5.4)
Aggressive reaction	18 (10.6)	9 (5.4)
Coughing	5 (2.9)	9 (5.4)
Headache	11 (6.5)	8 (4.8)
Infection	12 (7.1)	6 (3.6)
Diarrhea	22 (12.9)	5 (3.0)
Dyskinesia	9 (5.3)	1 (0.6)
Total patients with adverse event	157 (92.4)	157 (94.0)

[a]World Health Organization preferred terms.

Serious adverse events, defined as life-threatening, requiring hospitalization, or resulting in significant disability or incapacity, were experienced by 15 patients (8.8%) in the placebo group and 28 patients (16.8%) in the risperidone group. The most frequent serious adverse event was injury, followed by cerebrovascular disorder, pneumonia, and accidental "overdose." Regarding cerebrovascular adverse events, in the risperidone group, 5 patients suffered a stroke and 1 had a transient ischemic attack (TIA). Of these patients, aged between 79 and 89 years, 5 had vascular dementia or mixed AD/vascular dementia and 1 had AD. All had medical histories of significant predisposing factors for cerebrovascular events: hypertension (5/6), atrial fibrillation (4/6), and diabetes mellitus (1/6).

Extrapyramidal Symptoms

The ESRS total scores in the 2 groups were similar at baseline. At endpoint, these scores had increased relative to baseline in both groups. Although this increase was significant in the risperidone group ($p = .043$), there was no significant difference in the total ESRS score between placebo and risperidone at endpoint (Table 5).

A total of 27 patients (15.9%) in the placebo group and 39 (23.4%) in the risperidone group had 1 or more EPS-like adverse event. In these patients, the average median time to first incidence of an EPS-related adverse event was 75 days for the placebo group and 78 days for the risperidone group. Three patients, all of whom were in the

Table 5. Summary of ESRS Scores at Baseline and Changes From Baseline at Endpoint at All Sites

	Placebo		Risperidone		
ESRS	Baseline Mean (SE)[a]	Endpoint Mean Change (SE)[a]	Baseline Mean (SE)[a]	Endpoint Mean Change (SE)[a]	p Value[b]
Total ESRS questionnaire	4.9 (0.49)	0.5 (0.48)	4.5 (0.40)	0.7 (0.35)*	.407
Subscales					
Bucco-linguo-masticatory factor	0.9 (0.17)	–0.1 (0.17)	1.0 (0.18)	–0.0 (0.17)	.440
Parkinsonism/dystonia total	10.4 (0.54)	–0.7 (0.42)	11.0 (0.59)	1.6 (0.47)**	< .001
Parkinsonism total score	10.2 (0.52)	–0.6 (0.40)	10.7 (0.56)	1.5 (0.45)**	< .001

[a]Higher scores imply worsening condition.
[b]Test for no difference between treatments from ANCOVA model with factors for treatment, baseline score (as covariate), and investigator.
*p < .050 vs. baseline.
**p < .001 vs. baseline.
Abbreviation: ESRS = Extrapyramidal Symptom Rating Scale.

risperidone group, developed tardive dyskinesia after 1, 27, and 29 days of risperidone treatment. They had previously received conventional antipsychotic medication (1 patient received chlorpromazine, another haloperidol, and a third thioridazine). The initiation of anti-EPS medication was similar in the 2 treatment groups: 3 patients (1.8%) in the placebo group and 3 patients (1.8%) in the risperidone group. The median time to first initiation of anti-EPS medication was 1 day for the placebo group and 29 days for the risperidone group.

Concomitant Treatment

Treatment with benzodiazepines (short-acting hypnotics) was initiated in significantly more patients in the placebo group (N = 113, 66.5%) than in the risperidone group (N = 94, 56.3%; p = .029).

Vital Signs

A total of 4 patients (2.4%) in the placebo group and 5 patients (3.0%) in the risperidone group had hypotension reported as an adverse event during the treatment phase of the study. Three patients (1.8%) in the placebo group and 4 patients (2.4%) in the risperidone group experienced hypertension during the treatment phase of the study. No consistent changes in blood chemistry or hematology were observed.

Decreases in weight and body mass index from screening were statistically significant (p < .001) in the placebo but not in the risperidone group, resulting in significant (p < .05) differences between the placebo and risperidone groups at endpoint.

DISCUSSION

This was a 12-week, randomized, double-blind, placebo-controlled, parallel-group, investigator-initiated, multicenter trial comparing risperidone and placebo in the treatment of aggression, agitation, and psychosis in an elderly nursing-home population. Contrary to previous studies,[18,19] which included patients with general behavioral disturbances related to dementia, this study specifically enrolled elderly patients with dementia displaying aggressive behavior. As assessed by the CMAI total aggression subscale, risperidone, when administered orally using a flexible dosage schedule (0.5–2.0 mg/day in divided doses), was significantly more effective than placebo in reducing aggression. This improvement was noted by week 4 and continued throughout treatment. A significant reduction in aggressive behavior was also observed in subgroups of patients with and without psychosis and in those who did not experience somnolence during the trial period, indicating that reduction in aggressive behavior is a direct effect of risperidone and not secondary to an antipsychotic effect or to sedation.

A significant improvement was also seen for nonaggressive, agitated behaviors, as measured on the total non-aggression subscale of the CMAI. Furthermore, BEHAVE-AD total scores and investigator and caregiver CGI scores showed a significantly better outcome for risperidone with respect to overall behavioral disturbances related to dementia, without a negative effect on cognitive function as assessed by MMSE and FAST scores. These results were remarkably consistent with the findings from previous studies[18,19] and confirm the efficacy of risperidone in treating nursing-home patients with aggression, agitation, and psychosis related to dementia. Further support for the efficacy of risperidone on reducing behavioral disturbances came from the higher level of placebo medication administered.

The most frequent adverse events in the total population were injuries, falls, somnolence, and urinary tract infections. In general, even the adverse events that occurred more frequently in the risperidone group than in the placebo group, including somnolence, EPS, tremor, and abnormal gait, had a relatively low incidence, particularly compared with the incidence that has been observed with conventional antipsychotics in previous studies.[18,27,28] Cerebrovascular adverse events were reported in more patients treated with risperidone than with placebo. Patients suffering a cerebrovascular event had significant predisposing medical risk factors. This study, however, was not designed to stratify by risk factor across treatment and

placebo groups. A total of 10 patients, 4 in the placebo group and 6 in the risperidone group, died during the trial, most commonly because of pneumonia. The relationship between risperidone and each of the adverse events leading to death was recorded by the investigator either as "none" or "doubtful."

The incidence of EPS associated with risperidone at a mean dosage of 1 mg/day was low (i.e., 6% of risperidone-treated patients compared with 3% of placebo-treated patients). The overall incidence of any EPS-like adverse event (including EPS, dystonia, tremor, etc.) was not significantly different in risperidone- and placebo-treated patients (23% versus 16%, respectively). Only 3 patients in each group initiated treatment with anti-EPS medication. Although scores on several subscales of the ESRS were significantly higher for risperidone-treated patients than placebo-treated patients at endpoint, there were no statistically significant differences between the groups for total ESRS. Three patients in the risperidone group developed tardive dyskinesia, which may have been related to previous psychotropic treatment. These findings confirm those found in earlier trials, in which it was concluded that the incidence of EPS with risperidone at 1 mg/day was similar to placebo.[18,19] As the risk of EPS is generally found to be greater with conventional neuroleptics,[16–18] and as EPS are particularly troublesome among the elderly, this finding would support risperidone as a more suitable antipsychotic than conventional neuroleptics for use in elderly patients with dementia confounded by behavioral and psychological symptoms.

CONCLUSION

The results of this trial demonstrate that treatment with risperidone (mean = 0.95 mg/day) results in a significant reduction in aggression, agitation, and psychosis associated with several forms of dementia as measured by both the CMAI and the BEHAVE-AD and validated as clinically meaningful by a significant improvement in CGI scores. The reduction in aggression was not secondary to sedation or to the antipsychotic properties of risperidone, indicating a direct effect of risperidone on this behavior.

Drug names: chlorpromazine (Thorazine and others), haloperidol (Haldol and others), oxazepam (Serax and others), risperidone (Risperdal).

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