Risperidone in the Elderly: A Pharmacoepidemiologic Study

Carlos A. Zarate, Jr., M.D., Ross J. Baldessarini, M.D., Arthur J. Siegel, M.D., Ataru Nakamura, M.D., Jane McDonald, M.B.A., R.Ph., Lou Ann Muir-Hutchinson, M.P.H., Tanya Cherkerzian, and Mauricio Tohen, M.D., Dr. P.H.

Background: The possibly limited adverse effects of risperidone encourage interest in its use in geriatric patients.

Method: Medical records of 122 hospitalized psychogeriatric patients (≥ 65 years old) newly treated with risperidone were reviewed and scored for indications, doses, and effects of this novel neuroleptic.

Results: Subjects (83 women, 39 men), mean ± SD age = 76.5 ± 6.8 years (range, 65–95), were given risperidone for agitation or psychosis associated with dementia (53%), a major mood disorder (29%), or other disorders (18%). Most (77%) were also medically ill and received other psychotropic (76%) or cardiovascular agents (70%). Daily doses of risperidone averaged 1.6 ± 1.1 mg (range, 0.25–8.0) (0.025 mg/kg body wt.); 78% received 2.0 mg. Risperidone appeared to be effective in 85% of cases, but 18% were discontinued due to intolerability (11%) or inefficacy (7%). Adverse events occurred in 32% of the patients (36% of those discontinued). These adverse events included hypotension (29%) or symptomatic orthostasis (10%), cardiac arrest (1.6%) with fatality (0.8%), and extrapyramidal effects (11%) or delirium (1.6%). Benefits were associated with younger age and male gender, but not risperidone dose. Adverse effects were associated with cardiovascular disease and its treatment, cotreatment with an SRI antidepressant or valproate, and relatively rapid dose increases.

Conclusion: Risperidone appeared to be effective and may be safe for many elderly psychiatric patients with comorbid medical conditions provided that doses are low and increased slowly. Particular caution is advised in the presence of cardiovascular disease or cotreatment with other psychotropic agents.

(J Clin Psychiatry 1997;58:311–317)

Received Aug. 8, 1996; accepted April 2, 1997. From the Pharmacy & Therapeutics Committee (Drs. Zarate, Baldessarini, Siegel, and Tohen and Mss. McDonald and Muir-Hutchinson) and the Pharmacoepidemiology Center, McLean Hospital, Belmont (Drs. Zarate, Baldessarini, Nakamura, and Tohen and Ms. Cherkerzian); the Consolidated Department of Psychiatry (Drs. Zarate, Baldessarini, Nakamura, and Tohen) and the Neuroscience Program, Harvard Medical School (Dr. Baldessarini); and the Department of Epidemiology, Harvard School of Public Health, Boston (Dr. Tohen), Mass.

Supported in part by the American Psychiatric Association's Program for Minority Research Training in Psychiatry, United States Public Health Service (USPHS) grant MH-19126 and the Harvard Medical School Ethel Dupont-Warren and Livingston Fellowships (Dr. Zarate); by the McLean Pharmacoepidemiology Center Fund, USPHS grants MH-31154 and MH-47370, a grant from the Bruce J. Anderson Foundation, and the McLean Private Donors Neuropharmacology Research Fund (Dr. Baldessarini).

Reprint requests to: Carlos A. Zarate, Jr., M.D., McLean Hospital, 115 Mill Street, Belmont, MA 02178.

Neuroleptics are frequently prescribed for psychotic disorders as well as agitation and other behavioral disturbances in the elderly.[1,2] Adverse effects of such drugs are common in geriatric patients[3,4] and include orthostatic hypotension that results in falls and fractures,[5,6] delirium,[7] acute extrapyramidal symptoms (EPS)[2] or tardive dyskinesia, and autonomic dysfunction accompanied by urinary retention, constipation, or acute glaucoma.[2,8] In patients 65 years or older, the risks for acute EPS as well as for tardive dyskinesia are about 50%.[9,10] Furthermore, the efficacy of these widely used agents, such as for psychosis, mania, or agitation, lacks support by controlled research in the elderly.[1] Effective agents that limit some of the adverse effects of antipsychotic agents would be of great value.

Risperidone, a benzisoxazole derivative, is a new antipsychotic drug with high affinity and antagonistic action at serotonin 5-HT_2 as well as D_2 dopamine receptors. It is effective in the treatment of schizophrenia in young adults and has a limited risk of drug-induced EPS at low doses.[11] There is little information regarding its effectiveness and safety in the elderly, particularly in the large population of psychogeriatric patients with comorbid medical disorders who require other medications. Available information on the use of risperidone in geriatric patients is based primarily on clinical experience and a few

case reports.[12–24] Accordingly, we evaluated the safety and efficacy of risperidone in a large sample of hospitalized elderly psychiatric patients to develop guidelines for its use in this population.

METHOD

We identified all patients consecutively admitted to McLean Hospital over 14 months between February 1994 and May 1995, aged 65 years or older, who were newly treated with risperidone. A total of 795 patients had received risperidone in that period; of those, 122 (15.3%) were 65 or older. These 122 medical records were reviewed to determine age, gender, DSM-IV discharge diagnosis, length of illness, medical and neurologic conditions, mean and maximum daily dose and dose/weight of risperidone, and duration of risperidone use.

To evaluate initial dosing of risperidone, we identified "slow," "intermediate," and "rapid" dose increases as rates, respectively, below, at, or above the schedule recommended by the manufacturer *in the elderly*[25] as an initial dose of 0.5 mg twice on Day 1, with daily dosage increases of 0.5 b.i.d. to 1.5 b.i.d. and weekly increases by 1.0 mg/day thereafter. In addition, the medical records were reviewed for body weight, systolic and diastolic blood pressure (BP) readings before and during risperidone treatment, as well as for results of laboratory tests, electrocardiogram (ECG), and adverse events, including hypotension, clinical evidence of cardiac dysfunction, extrapyramidal side effects (EPS), excess sedation, and delirium. Significant hypotension was defined as a decrease of 15 mm Hg in sitting systolic BP during versus before risperidone treatment. Symptomatic orthostasis was defined as syncope, falls, or dizziness leading to a BP determination that demonstrated a 25 mm Hg systolic or 10 mm Hg diastolic decrease in BP on shifting from a horizontal to a standing position.

Efficacy of risperidone was assessed with the Clinical Global Impressions-Improvement (CGI-I) scale.[26] High intraclass correlation coefficients were previously obtained with this scale in similar application ($\kappa \geq .80$).[27] This information was supplemented with detailed reviews of all patients treated with risperidone by the McLean Hospital Pharmacy and Therapeutics Committee as part of the Continuous Quality Improvement program to monitor adverse drug reactions (ADRs) associated with new drugs.[28] In this program, a clinical pharmacist investigator visited each inpatient psychiatric unit several times a week to solicit voluntary reports from personnel regarding possible ADRs associated with risperidone. In addition, the investigator reviewed each risperidone-treated patient's hospital record for evidence of complications related to drug use. All ADRs identified in association with the use of risperidone were reviewed by the ADR Continuous Quality Improvement team (consisting of a psychiatrist, nurse, internist, and pharmacist) for a final determination of the likelihood that the ADR was related to risperidone.

Table 1. Doses of Risperidone in 122 Psychogeriatric Patients

Dose	Mean	SD	Range
Maximum (mg/d)	2.0	1.6	0.5–8.0
All subjects			
mg/d	1.6	1.1	0.25–5.9
µg/kg/d	25.3	17.4	5–89
Women			
mg/d	1.4	0.9	0.5–4.8
µg/kg/d	23.6	15.7	7–89
Men			
mg/d	2.0	1.5	0.5–5.9[a]
µg/kg/d	29.2	20.3	5–75[b]

[a]mg/d of risperidone men vs women, unpaired t = 2.9, df = 120, p = .005.
[b]µg/kg/d of risperidone men vs women, unpaired t = 1.7, df = 120, p = .097.

Categorical variables were compared with contingency tables (chi-square), or Fisher's exact test (p value) when expected cell sizes were < 5; continuous variables were analyzed by Student's t test. Statistical significance required $p < .05$ in two-tailed tests at defined degrees of freedom (df). Data are reported as means ± SD unless stated otherwise.

RESULTS

Characteristics of Subjects

The 122 psychiatrically hospitalized geropsychiatric subjects were 83 women and 39 men, aged 76.5 ± 6.8 years (range, 65–95) who had been psychiatrically ill for 12.9 ± 16.7 years. Their index hospitalization lasted 20.9 ± 14.7 days (range, 3–90). The most common DSM-IV psychiatric diagnoses were dementia (52.5%); major depression with psychotic features (16.4%); bipolar disorder, manic or mixed, with psychotic features (13.1%); and schizophrenia (8.2%). Treatment with risperidone lasted, on average, 12.9 ± 14.7 days (range, 1–58). Most of the subjects also had medical or neurologic disorders that complicated their clinical management and often required use of multiple medications; 77.0% had at least one comorbid medical illness. The most common medical disorders by organ system were cardiovascular (69.7%); neurologic, not dementia (22.1%); endocrinological (17.2%); pulmonary (17.2%); renal (11.5%); and gastrointestinal (8.2%).

Medications Received

The mean daily dose of risperidone was 1.6 ± 1.1 mg (2.0 ± 1.5 in men vs. 1.4 ± 0.9 in women; unpaired t = 2.87, df = 120, p = .005); 77.9% of patients received 2 mg/day or less (Table 1). Body weight averaged 60.0 ± 13.6 kg in women and 69.5 ± 12.9 kg in men. Men tended to receive slightly higher weight-corrected daily

doses of risperidone (29.2 ± 20.3 vs. 23.6 ± 15.7 μg/kg; t = 1.67, df = 120, p = .097). At least one other psychotropic agent was received by 93 (76.2%) of 122 subjects, in rank-order of frequency: antidepressants (25.4% [N = 31] includes serotonin reuptake inhibitors [N = 21] and tricyclics [N = 10]); sedative-anxiolytics (15.6%); anticonvulsants (14.8% [N = 18] includes valproate [N = 11], phenytoin [N = 4], and carbamazepine [N = 3]); lithium (9.0%); anticholinergics (7.4%); or another neuroleptic (4.1%). A majority (83.6%) also received at least one medicinal agent for comorbid medical illness, particularly cardiovascular conditions, for which 85 (69.7%) of 122 were treated. The most common cardiovascular agents received were diuretics (18.9%), calcium channel blockers (18.0%), β-adrenergic blockers (10.7%), and angiotensin-converting enzyme (ACE) inhibitors (8.2%). The most common non-cardiovascular agents received were antibiotics (9.8%), salicylates (9.0%), and levothyroxine (5.7%).

Indications for Treatment With Risperidone

Reasons for using risperidone were stated in 117 (95.9%) of 122 cases. The reasons included lack of previous response to (45.1%) or intolerance of standard neuroleptics (20.5%), or both (13.1%), or failure to respond to trials of other psychotropic agents including sedatives and mood stabilizers (16.4%). In 6 patients (4.9%), risperidone was employed electively in newly treated cases. Prominent target symptoms for which risperidone was prescribed were explicitly documented in all but 2 cases (a total of 98.4% of the patients). In rank-order of frequency, the indications included psychosis (41.8% [N = 51], with delusions [N = 20], hallucinations [N = 17], or both [N = 14]) or agitation with deteriorating behavioral status (56.6% [N = 69], with varying degrees of assaultiveness [N = 26], verbal outbursts [N = 21], poor socialization [N = 12], or poor self-care [N = 10]).

Effectiveness of Risperidone

The efficacy of risperidone was determined in 108 (88.5%) of 122 patients who did not discontinue the drug because of side effects. Risperidone appeared to be effective in 85.2% of these 108 patients. Response rates for this sample as determined by the 7-point CGI-I scale applied to clinical records were (1) much improved, 23.6%; (2) improved, 36.1%; (3) minimally improved, 25.9%; (4) unchanged, 10.2%; (5) worse, 3.7%; (6) much worse, 0.9%; and (7) very much worse, 0%. In the most common diagnostic group, demented patients with agitated or psychotic features, 46 (82.1%) of 56 were rated as either "much improved," "improved," or "minimally improved" with risperidone treatment. There was no difference in response in patients treated at clinically determined daily doses of risperidone of 2 mg or less, compared with patients receiving higher doses of risperidone ($\chi^2 = 4.31$, df = 5, p = .50). Compared with patients displaying worse-to-minimal improvement, patients much-to-very much improved with risperidone were more likely to be younger and of male gender. No other variable examined (psychiatric diagnosis, concurrent medical and neurologic illness, duration of illness, risperidone dose, and duration of risperidone trial) was associated with a poor response to risperidone, as defined by a score of 3 to 7 on the CGI-I scale.

Table 2. Adverse Events Associated With Risperidone Treatment in 122 Psychogeriatric Patients*†

Problem	Number of Adverse Events	Proportion (%)
Cardiovascular	59	48.4
Hypotension	56	45.9
Nonsymptomatic	35	28.7
Symptomatic orthostasis	12	9.8
Dizziness	6	4.9
Syncope	1	0.8
Other falls	2	1.6
Cardiac arrhythmia	3	2.5
Arrest	2	1.6
Resuscitated	1	0.8
Fatal	1	0.8
Depressed ECG conduction	1	0.8
CNS-related reactions	24	19.7
Extrapyramidal side effects (new)	13	10.7
Tremor	7	5.7
Bradykinesia/rigidity	5	4.1
Akathisia	1	0.8
Excessive sedation	4	3.3
Delirium	2	1.6
Headache	2	1.6
Seizures	1	0.8
New agitation	1	0.8
New depression	1	0.8
Gastrointestinal/metabolic	8	6.6
Constipation	4	3.3
Nausea	2	1.6
Heartburn	1	0.8
Hypoglycemia	1	0.8

*Note that extrapyramidal symptoms (EPS), presumably due to previous neuroleptic treatment, were also present in 20 patients at the time of starting risperidone, and another 4 also were diagnosed with Parkinson's disease. Only newly emerging EPS are recorded here.
†Thirty-nine patients (32.0%) experienced adverse events. Most patients (24.6%) had more than one side effect; 11.5% of patients had > 1 adverse event; 9.0% had > 2; and 4.1% had > 3.

Adverse Events

At least one adverse effect was associated with use of risperidone in 32.0% (39/122) of the study sample (Table 2). Most common problems were hypotension (45.9%) at rest (28.7%) or on standing (9.8%) and acute neurologic side effects (10.7%: tremor > bradykinesia or rigidity > akathisia) (Table 2). Only 1 patient experienced clinically asymptomatic hypoglycemia (fasting blood glucose level before and during risperidone was 112 and 48 mg/dL, respectively). No other alterations in blood chemistry, including electrolytes, or hematology were recorded.

In the 17 (43.6%) of 39 patients with side effects, the daily dose of risperidone was reduced because of adverse

events by an average of 19.0%, from 2.1 ± 1.8 to 1.7 ± 1.3 mg (paired $t = 5.18$, $df = 65$, $p = .0001$). The mean daily doses of risperidone at the time of hypotension and acute EPS, respectively, were 1.8 ± 1.4 and 2.0 ± 1.2 mg; these doses did not differ from those in subjects having no such adverse effects (respectively, $t = 1.25$ and 1.36, both $df = 120$, both N.S.). Moreover, there was no greater risk of hypotension or EPS at clinically determined daily doses of risperidone below or ≥ 2 mg ($\chi^2 = 0.37$, $df = 1$, $p = .54$ and Fisher's exact $p = .39$, respectively). Patients given risperidone in combination with an SRI antidepressant or valproate, both of which can increase serum concentrations of neuroleptics,[28] tended to be more likely to develop acute EPS than those not treated with one of these combinations (7/39 vs. 6/83; $\chi^2 = 3.2$, $df = 1$, $p = .074$). There was an insignificantly lower EPS risk in patients aged 65 to 75 versus 76 to 95 years (5/59 [8.5%] vs. 8/63 [12.7%]; $\chi^2 = 0.57$, $df = 1$, $p = .45$), and the daily dose of risperidone was slightly lower in the older subgroup (1.3 ± 0.8 vs. 1.9 ± 1.0 mg; unpaired $t = 2.6$, $df = 120$, $p = .01$). Among 20 patients who had neurologic abnormalities associated with other neuroleptics prior to risperidone therapy, such symptoms may have diminished somewhat, since antiparkinsonian agents were discontinued in 40% of these patients.

The mean systolic BP prior to risperidone treatment (131.9 ± 18.9 mm Hg) fell by 5.1% during risperidone treatment (to 125.2 ± 14.1 mm Hg; paired $t = 4.6$, $df = 121$, $p < .0001$). Diastolic BP decreased by 9.7% (from 77.7 ± 10.8 to 70.2 ± 8.1 mm Hg; paired $t = 6.6$, $df = 121$, $p < .0001$). Of the 12 patients who experienced symptomatic orthostatic hypotension, this side effect arose in 3.2 ± 3.2 days (range, 1–13) at a mean daily dose of 1.6 ± 1.4 mg of risperidone. Of the 12 patients (9.8%) with symptomatic orthostasis, 5 (41.7%) were taking an antihypertensive agent (2 a diuretic, 2 a calcium channel blocker, and 1 an ACE inhibitor), and 7 (58.3%) were taking an agent that can increase serum neuroleptic levels (an SRI or valproate).

Cardiac arrest occurred in 2 (1.6%) of 122 patients during treatment with risperidone. An 80-year-old woman suffering from bipolar disorder, senile dementia of the Alzheimer's type, stable insulin-dependent diabetes, and no known cardiac disease was sedated for several days while taking trazodone 50 mg q.h.s., lorazepam 0.5 mg/day p.r.n., and risperidone 2 mg/day. She suddenly collapsed with ECG-documented complete heart block followed by cardiac arrest and death (autopsy not obtained). Shortly before she was found unresponsive, she had been witnessed to be choking and exhibiting an oculogyric crisis. Her condition stabilized, and she was transferred to a local general hospital for cardiac evaluation. Further inquiry about previous medication trials revealed that she had been treated with risperidone for 6 months and had not had significant side effects. A 69-year-old woman suffering from mixed bipolar disorder, mild aortic insufficiency, and mitral valve prolapse took divided doses of risperidone (0.5 mg twice daily) in addition to paroxetine 20 mg/day, divalproex sodium 250 mg b.i.d., benztropine 0.5 mg b.i.d., and clonazepam 0.5 mg q.a.m. and 1.0 mg at bedtime. She experienced no obvious adverse effects for 7 days. On Day 8, she became nonresponsive, was found to be in ventricular fibrillation, and was resuscitated.

Delirium occurred in 2 (1.6%) of 122 patients who were both taking more than four other medications in addition to risperidone 1 to 2 mg/day. The first received benztropine, metoprolol, nifedipine, oxybutynin, and ranitidine; the second, aspirin, benztropine, glyburide, nifedipine, and divalproex sodium. Delirium resolved in both cases within 24 hours of lowering the dose of risperidone by a mean of 30%. One patient with no history of epilepsy suffered a grand mal seizure while taking risperidone. There were no cases of tardive dyskinesia or neuroleptic malignant syndrome.

Overall, patients undergoing a slow increase of the dose of risperidone, as defined in the Method section (N = 55), were less likely to have an adverse drug event than those undergoing either intermediate (N = 38) or rapid (N = 29) increases (40.7%, 70.3%, 61.5%, respectively; $\chi^2 = 12.7$, $df = 2$, $p = .002$).

Discontinuation of Risperidone

Risperidone was discontinued in 22 (18.0%) of 122 of the subjects: in 14 (11.4%) due to side effects and 8 (6.6%) due to lack of efficacy. Adverse effects leading to discontinuation were symptomatic orthostasis (N = 5), EPS (N = 3), sedation (N = 2), cardiac arrhythmia (N = 2), seizure (N = 1), and nausea (N = 1). Of the patients with symptomatic orthostatic hypotension, 5 (41.7%) of 12 eventually discontinued risperidone, compared to a discontinuation risk of 9 (8.2%) of 110 without this adverse effect ($\chi^2 = 11.9$, $df = 1$, $p = .0005$). Patients undergoing relatively rapid initial increases of risperidone dose, as defined in the Method section, were more likely to discontinue risperidone because of an adverse event than those undergoing either intermediate or slow increases (21.1%, 7.9%, 7.3%, respectively; $\chi^2 = 6.33$, $df = 2$, $p = .04$).

DISCUSSION

Methodological limitations constrain the security and generalizability of the present preliminary, uncontrolled observations of clinical experience in our institution dating from the general release of risperidone in 1994. Data were collected retrospectively by reviewing medical records, and adverse events may have been underreported. However, in cases of clinically important adverse effects, the data collected by chart review were compared to, and found congruent with, information gath-

ered by extensive case reviews obtained by a Continuous Quality Improvement program that involves the departments of psychiatry, medicine, nursing, and pharmacy. In addition, the role of risperidone in some adverse events is unclear since all 122 subjects in the present study were elderly (aged 65–95 years) and, in addition to having acute, and usually psychotic, psychiatric illness, most had medical and neurologic illness or disability and were exposed to several medicinal agents simultaneously. Additional research is required to provide more secure estimates of the risks of specific adverse events in elderly patients treated with risperidone.

There were encouraging findings concerning evidently beneficial effects of risperidone treatment in a broad range of geropsychiatric disorders, characterized by reduction in agitation, psychotic symptoms, and disorderly behavior. Diagnoses included dementia, schizophrenia, schizoaffective disorder, bipolar disorder or major depression with psychotic features, delusional disorder, and psychotic disorder not otherwise specified. Overall, more than 85% of the 122 subjects treated with risperidone appeared to benefit appreciably, and 59% benefited moderately or markedly, based on the CGI-I ratings we applied to their medical records. Moreover, the drug was generally well tolerated in this elderly sample, provided that dosing was cautious and conservative. In the limited previous clinical assessments of risperidone in the elderly, for daily doses up to 1 mg, risperidone was considered "very helpful" over a 6-month period in 41% of 64 nursing home residents (mean age = 80.0 years), as determined by a nursing questionnaire.[14–16,18]

We found that 32.0% (39/122) of the present geriatric subjects (mean age = 76.5 years) experienced at least one adverse event. These findings accord well with a similar reported incidence of adverse events in 40.1% of 22 elderly patients (mean age = 69.8 years) treated with risperidone up to 6 mg daily for 4 weeks in a recent open-label study.[14] The most common effects in the present cases were probable hypotension (45.9% overall incidence), including dizziness, symptomatic hypotension, or syncope (15.6%). Although 2 patients (1.6%) had fallen, neither fractures nor other serious physical injuries were recorded. However, there were 2 instances of life-threatening or fatal cardiac arrhythmias (1.6% incidence), which may or may not be related to either cardiovascular or CNS actions of risperidone associated with the high risk of hypotension (45.9%) in the study sample. Extrapyramidal side effects (10.7%) and other CNS-based adverse effects (excess sedation, delirium, seizures, headaches, and new agitation or depression; 9.0%) also were not infrequent (19.7% overall incidence). These relatively high rates for cardiovascular and CNS-based adverse effects may be characteristic of responses of the elderly to central depressants. The risks may be particularly associated with the simultaneous use of other agents, including hypotension-inducing drugs (such as calcium channel blockers or ACE inhibitors) or neuroleptic-potentiating agents (such as SRI antidepressants or valproate).[29]

This experience contrasts strikingly to the relatively low risk of such effects in young adults, even at much greater doses than the low daily mean of 1.6 mg (25 μg/kg) received by the present elderly subjects. In over 2600 younger adults with a psychotic disorder treated with standard doses of risperidone (typically, 4–8 mg/day), hypotension was uncommon (0.1%–1% incidence) and syncope was rare (0.2%).[22] In geriatric patients, the reported incidence of hypotension associated with risperidone has been variable, ranging from 11.0% in 18 hospitalized elderly patients given 0.5 to 4.0 mg/day,[16] or 13.7% in 22 hospitalized patients in doses up to 6 mg/day,[14] to as high as 36.4% in 11 patients aged 61 to 79 given 0.5 to 3.0 mg/day.[18] This accumulated experience suggests that either mild or symptomatic hypotension has been observed in at least 64/173 elderly patients given risperidone (37.0% overall incidence[14,16,18] and in our study). As in the present cases, severe hypotensive reactions have been particularly likely among patients being treated with antihypertensive agents while taking risperidone.[18] Differences in these several estimates may reflect differences in definition of hypotension and its ascertainment, as well as variance in the use of other cardiovascular or neurodepressant medications, and the effects of unreliably small samples.

The incidence of EPS with risperidone at daily doses below 16 mg (17%) in 2600 young adults was similar to that found in placebo groups (16%), but as high as 34% at 16 mg.[25] In 22 geriatric patients treated with risperidone up to 6 mg daily, the reported risk of EPS was 9.1%,[14] compared with the recorded incidence of 10.7% for new-onset EPS in our patients and an incidence of 27.0% that includes cases of preexisting EPS in the present study. EPS or other adverse CNS-based effects of risperidone may be characteristic of the elderly, and perhaps the very young as well.[30] On the other hand, a more favorable perspective is that 40% of the present 20 subjects with preexisting EPS associated with other neuroleptic agents neurologically tolerated and evidently benefited from risperidone treatment at low doses (1.34 ± 0.82 mg/day) without continued use of antiparkinsonian agents, and EPS severe enough to require discontinuation of risperidone arose in only 4 (3.3%) of 122 subjects. Thus, very cautious dosing with risperidone may be tolerated at the extremes of the age range.[30]

Due to cardiovascular as well as CNS adverse effects, the manufacturer's recommended dosing for risperidone that specifies daily increases of 1 mg twice daily to reach 6 mg/day within 3 days is probably excessive for many geriatric (and pediatric) patients, and even dosing at half that level or rate, as recommended by the manufacturer for geriatric use, may be excessive for many elderly patients.[25,30] We found that 43.6% of geropsychiatric

patients required lower doses of risperidone because of adverse events, even after following already conservative dosing up to a most frequent daily maximum of 2.0 mg.

The present findings indicate that slowly increased doses of risperidone were better tolerated and suggest the following tentative guidelines for initiating risperidone therapy in psychogeriatric patients. (1) Elderly, infirm patients require a thoughtful medical evaluation before starting treatment with risperidone. (2) All other drugs, and particularly cardiovascular and CNS depressants, should be reviewed critically for elimination or reduction to minimum effective doses before risperidone is added. (3) Warning signs and symptoms of impending risperidone intolerance include excessive sedation, confusion, dizziness or unsteadiness, and bradykinesia. Sitting versus standing blood pressure should be monitored scrupulously until risperidone treatment is stabilized and its tolerability in individual patients assured. (4) Suggested initial oral doses of risperidone may be as low as 125 µg once or twice daily, with increments of 125 µg once or twice daily at intervals of not less than 3 days. Dosing may need to be even more conservative, or the use of risperidone reconsidered, if other agents known or suspected to produce pharmacodynamic interactions with risperidone (e.g., adrenergic antagonists, calcium channel blockers, ACE inhibitors, other vasodilators, diuretics) are also employed.[30] If agents with known or suspected pharmacokinetic interactions are coadministered with risperidone (e.g., SRIs and perhaps other antidepressants, valproate), cautious dosing is appropriate.[29,30] Ideally, as methods for therapeutic drug monitoring with risperidone become better established, dosing with the risk of drug interactions might be guided by use of highly sensitive chemical assays of risperidone and its major, active 9-hydroxy metabolite.[25,31] In the present geriatric series, many patients responded to daily doses of risperidone of only 1 to 2 mg; rarely were doses as high as 4 to 6 mg required or tolerated (Table 1).

In view of the evidently important and potentially dangerous hypotensive effect of risperidone in the elderly, if it is used at all, extreme caution should be used when prescribing risperidone for patients with preexisting cardiac disease or ongoing treatment for hypertension, as well as those with common dehydration and suspected volume depletion. If a clinically significant or symptomatic decrease in blood pressure occurs, and it is considered necessary to continue risperidone, a reduction in the dose or discontinuation of the antihypertensive drug should be considered, and pulse and blood pressure should be monitored closely.

In conclusion, risperidone was effective and generally well tolerated in low doses for the treatment of psychotic symptoms and behavioral disturbances in the majority of patients over age 65 in spite of high rates of comorbid medical illnesses and medically indicated use of other drugs. Among geriatric patients, a currently common starting dose of risperidone 0.5 mg twice daily may be excessive for many medically infirm psychogeriatric patients. EPS, sedation, and confusion were not uncommon, even at daily doses of risperidone of 2.0 mg or less. Moreover, clinically significant decreases in blood pressure were strikingly frequent, and occasionally dangerous, especially when risperidone was combined with an SRI antidepressant, valproate, or an antihypertensive drug. Further studies to assess the potential value of therapeutic drug monitoring for risperidone and to document its suspected pharmacokinetic interactions with other agents are required. Finally, the present experience and other findings discussed above suggest the need for unit dosage forms for risperidone smaller than the current scored 1.0-mg tablets, perhaps including scored tablets of lower doses and a liquid preparation. Our results also suggest that optimally tolerated doses of risperidone at the older age range may be much lower than in young adults. Moreover, the time required to increase risperidone to a maximum dose may need to be delayed well beyond 72 hours in the infirm elderly.

Drug names: benztropine (Cogentin and others), carbamazepine (Tegretol and others), clonazepam (Klonopin), divalproex sodium (Depakote), glyburide (Diabeta and others), levothyroxine (Synthroid and others), lorazepam (Ativan and others), metoprolol (Lopressor), nifedipine (Adalat, Procardia), oxybutynin (Ditropan, Dridase), paroxetine (Paxil), phenytoin (Dilantin and others), ranitidine (Zantac), risperidone (Risperdal), trazodone (Desyrel and others).

REFERENCES

1. Devanand DP, Levy SR. Neuroleptic treatment of agitation and psychosis in dementia. J Geriatr Psychiatry Neurol 1995;8(suppl 1):S18–S27
2. Peabody CA, Warner MD, Whiteford HA, et al. Neuroleptics and the elderly. J Am Geriatr Soc 1987;35:233–238
3. Baldessarini RJ. Chemotherapy in Psychiatry: Principles and Practice. 2nd ed. Cambridge, Mass: Harvard University Press; 1985
4. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Harden W, Rudin W, Molinoff PB, et al, eds. Goodman and Gilman's The Pharmacologic Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill; 1996:399–459
5. Blumenthal MD, Davie JW. Dizziness and falling in elderly psychiatric outpatients. Am J Psychiatry 1980;137:203–206
6. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987;316:363–369
7. Francis J Jr. Drug-induced delirium: diagnosis and treatment. CNS Drugs 1996;5:103–114
8. Raskind MA, Risse SC. Antipsychotic drugs and the elderly. J Clin Psychiatry 1986;47(5, suppl):17–22
9. Salz BL, Kane JM, Woerner MG, et al. Prospective study of tardive dyskinesia in the elderly. Psychopharmacol Bull 1989;25:52–56
10. Avorn J, Monane M, Everitt DE, et al. Clinical assessment of extrapyramidal signs in nursing home patients given antipsychotic medication. Arch Intern Med 1994;154:1113–1117
11. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;51:825–835
12. Aronson SM, Lingam VS, Hasanat KA. Risperidone in geropsychiatry: review of experience in two teaching public hospitals. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 23, 1995; Miami, Fla. Abstract NR267:127
13. Berman I, Pavlov-Rachov J, Losonczy MF, et al. Risperidone in elderly schizophrenic patients. In: Abstracts of the 34th Annual Meeting of the

New Clinical Drug Evaluation Unit; May 30–June 2, 1994; Orlando, Fla. Poster Abstract 57
14. Borison RL, Davidson M, Berman I. Risperidone treatment in elderly patients with schizophrenia or dementia. In: Abstracts of the 46th Annual Meeting of the Institute of Hospital and Community Psychiatry; May 6–12, 1995; Philadelphia, Pa. Poster Abstract 51
15. Goldberg RJ, Goldberg JS. Low-dose risperidone for dementia-related disturbed behavior in nursing homes. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 23, 1995; Miami, Fla. Abstract NR262:126
16. Prado N, Kramer-Ginsberg E, Kremen N, et al. Risperidone in dementia with behavioral disturbances. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 22, 1995; Miami, Fla. Abstract NR6:55
17. Reyntjens A, Heylen S, Gelders Y. Risperidone in the treatment of behavioral symptoms in psychogeriatric patients: a pilot clinical investigation [abstract]. Psychopharmacology 1988;96(1, suppl):335
18. Madhusoodanan S, Brenner R, Araujo L, et al. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995;56:514–518
19. Stanton SP, Wilson DR, Keck PE Jr, et al. Clinical predictors of acute risperidone response in elderly patients with schizophrenia and schizoaffective illnesses. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 6, 1996; New York, NY. Abstract NR117:99
20. Joshi UP, Joshi PM. Risperidone in geriatric patients with chronic psychoses and concurrent medical illnesses. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 7, 1996; New York, NY. Abstract NR387:173
21. Aronson SM, Lingam VS, Hasanat KA. Risperidone in the treatment of elderly psychiatric patients. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 8, 1996; New York, NY. Abstract NR493:204
22. Jeanblanc W, Davis YB. Risperidone for treating dementia-associated aggression [letter]. Am J Psychiatry 1995;152:1239
23. Raheja RK, Bharwani I, Penetrante AE. Efficacy of risperidone for behavioral disorders in the elderly: a clinical observation. J Geriatr Psychiatry Neurol 1995;8:159–161
24. Jeste DV, Eastham JH, Lacro JP, et al. Management of late-life psychosis. J Clin Psychiatry 1996;57(suppl 3):39–45
25. Risperdal (risperidone). Physicians' Desk Reference. 50th ed. Montvale, NJ: Medical Economics; 1996:1301–1305
26. Guy W. Clinical Global Impression. In: Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM)76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
27. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 1994;55:295–300
28. Continuous Quality Improvement update: teaming up to improve patient care quality. McLean This Week 1995; Mar 24:1–2
29. Meyer M, Baldessarini RJ, Goff D, et al. Clinically significant interactions of psychotropic drugs with antipsychotic agents. Drug Saf. In press
30. Baldessarini RJ, Teicher MH. Dosing of antipsychotic agents in pediatric populations. Journal of Child and Adolescent Psychopharmacology 1995; 5:1–4
31. Gupta J, Black DW, Smith DA. Risperidone: review of its pharmacology and therapeutic use in schizophrenia. Ann Clin Psychiatry 1994;6: 173–180