Risperidone in Dementia

Jacob E. Mintzer, MD; Subramoniam Madhusoodanan, MD; and Ronald Brenner, MD

Dementia is the most common psychiatric disorder in the elderly. In 1993, it was estimated that at least 4 million people in the United States had dementia and, of these, 70% had dementia of the Alzheimer type. Almost all patients will experience a behavioral disturbance during the course of the dementing illness. Behavioral and psychological symptoms of dementia (BPSD), including psychosis and changes in patterns of behavior, are seen in 50% of outpatients and in nearly 80% of nursing home residents with dementia.

The goals of treating BPSD depend on the precipitating causes, but the overall objective of intervention is to attenuate the excess disability associated with the dementia. BPSD are one cause of this excess disability and among patients already institutionalized, aggression and violence are difficult behaviors to manage. Before any drug therapy is initiated, however, the clinician needs to determine the causes of the disruptive behavior, such as underlying medical conditions, drug effects and interactions, infections, sensory disturbances, and unmet care needs. Any secondary medical conditions should be treated, and problematic medications adjusted or discontinued. In many cases, BPSD may respond positively to nonpharmacologic interventions, such as changes in the environment or in the approach or attitude of the caregiver. If these interventions fail, pharmacologic treatment may be necessary.

CONVENTIONAL NEUROLEPTICS

Conventional neuroleptics have been one pharmacologic strategy for treating BPSD. Salzman reported in 1987 that conventional neuroleptics "have consistent and reliable therapeutic effect in controlling agitation for elderly patients who are demented, psychotic, or both" and that no one agent was better than another. Ten years later, Finkel concluded that neuroleptics "have moderate, but limited, usefulness in treating dementia," confirming the results of the meta-analysis of 33 studies performed by Schneider et al.—therapeutic efficacy in agitated dementia was seen in 18% more of the patients treated with conventional neuroleptics than with placebo.

This group of medications, however, causes adverse effects, including extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), that are especially undesirable in the elderly population. In a recent study by Devanand et al., outpatients with Alzheimer's disease received a standard dose (2 to 3 mg/d) or a low dose (0.5 to 0.75 mg/d) of haloperidol or placebo for 6 weeks. A therapeutic response was seen in 55% to 60% of the patients receiving the standard dose of

Dr. Mintzer is from the Department of Psychiatry, Medical University of South Carolina, Charleston, South Carolina. Drs. Madhusoodanan and Brenner are from the Department of Psychiatry, State University of New York, Health Science Center at Brooklyn, and St. John's Episcopal Hospital, Far Rockaway, New York. Address reprint requests to Subramoniam Madhusoodanan, MD, St. John's Episcopal Hospital, 327 19th Street, Far Rockaway, NY 11691.

Dr. Mintzer has received grants/research support from Abbott, Eisei America, Inc., Eli Lilly, Janssen Research Foundation, the National Institute on Aging, Parke-Davis, Somerset Pharmaceuticals, SmithKline Beecham, Wyeth-Ayerst, and Zeneca. He is a paid consultant to Pine Rest Nursing Center in Michigan, Eli Lilly, Mt. Sinai Department of Psychiatry in New York, Abbott, AstraZeneca, and Bristol-Meyers Squibb. He is on the speaker's bureau of Janssen, AstraZeneca, Eisei, Eli Lilly, Abbott, Parke-Davis, and Pfizer. Dr. Madhusoodanan has conducted company-sponsored drug trials for Janssen Pharmaceuticals Inc., Pfizer, Bayer, Eli Lilly and Company, and Zeneca Pharmaceuticals. He is on the speaker's bureau for Janssen eldercare. Dr. Brenner participates as part of a multicenter site in research activities involving all manufacturers of atypical antipsychotics.
haloperidol, compared with 25% to 35% of the patients receiving the low dose or placebo. However, moderate to severe EPS were seen in 20% of the patients receiving the standard dose of haloperidol.

Conventional neuroleptics also have cardiovascular and anticholinergic effects and have been associated with the neuroleptic malignant syndrome and falls and fractures in the elderly.11

ATYPICAL ANTIPSYCHOTICS

Recently developed atypical antipsychotics include clozapine, risperidone, olanzapine, and quetiapine. These have been shown to be efficacious in elderly patients and less likely than conventional neuroleptics to cause EPS, TD,12 or other side effects such as orthostatic hypotension.13

Clinical Experience With Risperidone

The atypical antipsychotic risperidone has higher affinity for the 5-HT2 receptors than for the D2 receptors and has affinity for the α1- and α2-adrenergic receptors, but lacks affinity for the muscarinic receptors. In comparison with clozapine, risperidone has a higher binding affinity to 5-HT2 receptors at nanomolar concentrations.14,15 The beneficial effects of risperidone on aggressive behavior have been linked to its affinity for the serotonin receptors.16 In light of its receptor profile and its efficacy in schizophrenia and other psychoses, investigators hypothesized that risperidone might be particularly useful for managing the psychosis, agitation, and aggressive behaviors of elderly patients with dementia.16

Case Reports. In 5 case reports, risperidone reduced or eliminated dementia-related agitation and violence, as well as the psychotic symptoms. In the report by Jeanblanc and Davis,17 5 patients with dementia whose aggressive behavior had not been controlled with conventional neuroleptics were given risperidone. Within 7 to 10 days of starting risperidone at a dose of 1.5 to 2.5 mg/d, dementia-related agitation and violent behavior were eliminated or markedly decreased. In a retrospective chart review, Frenchman and Prince18 examined the effects of risperidone, haloperidol, and thioridazine on BPSD in 186 nursing home residents with Alzheimer’s dementia, senile dementia not otherwise specified, or organic brain syndrome. Improvement in the target behaviors of violence, shouting, delusions, paranoia, and pacing was seen in significantly more patients treated with risperidone than with either haloperidol or thioridazine. In a series of 11 patients with psychoses associated with a variety of disorders, Madhusoodanan et al.19 reported marked improvement (decreased hallucinations and agitation) in 2 of the patients with senile dementia treated with risperidone. Hermann et al.20 reported that 50% of 22 patients with dementia treated with risperidone experienced significant improvement in BPSD. Kopala and Honer21 reported that low doses of risperidone (1.5 mg/d) markedly decreased disruptive continuous vocalizations and caused no EPS in 2 women with severe dementia.

Open-Label Studies. Of 109 nursing home residents with BPSD of diverse etiologies, nurses rated the behavioral symptoms of 64% of these patients as moderately improved after 6 months of treatment with risperidone at a dose of 0.5 to 1 mg/d.22 Symptoms that responded to risperidone included agitation, verbal outbursts, physical aggression, depressed mood, anxiety, and sleep problems. Twenty-nine patients (27%) discontinued treatment because of inefficacy and 17 (16%) because of adverse effects (primarily oversedation). Overall, risperidone was well tolerated, even when used with multiple concurrent medications.

In a 9-week trial, Lavretsky and Sultzter23 reported that 15 patients with BPSD responded to low doses of risperidone, including 8 of 9 patients with probable Alzheimer’s disease, whose symptoms were rated as very much improved. Aggression responded within 3 weeks of treatment and agitation within 5 to 7 weeks. EPS reported in 54% of the patients responded to dose reduction and many of these patients had EPS at baseline. The modal optimal dose of risperidone was 0.5 mg/d.

Zarate et al.24 reviewed 122 hospital records of elderly patients with agitation or psychosis primarily associated with dementia or a major mood disorder newly treated with risperidone. Of the 108 patients who did not discontinue treatment, risperidone was effective in 85% as measured by
changes on the Clinical Global Impression scale. In the subgroup of 56 demented patients with agitation or psychotic features, 82% responded to risperidone. Adverse events included hypotension in 29% and EPS in 11%. Adverse events were associated with concomitant cardiovascular disease and its treatment, use of selective serotonin reuptake inhibitors or valproate, and rapid increases in the dose of risperidone.

**Controlled Studies.** Katz et al.\(^{13}\) have recently reported the results of a 12-week, randomized, double-blind, placebo-controlled, multicenter study evaluating the effects of three doses of risperidone (0.5, 1, and 2 mg/d) on symptoms of psychosis and aggressive behavior (verbal and physical). The study consisted of 624 patients (mean age 82.7 years) with severe dementia living in 40 long-term-care facilities. Seventy percent of the patients completed the trial.

Significant improvements in the severity and frequency of BPSD were noted as early as 2 weeks after the start of treatment (Figs. 1 and 2). At week 12, compared with placebo, treatment with 1 and 2 mg/d of risperidone resulted in significantly greater reductions in total scores on the Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD) rating scale (P = .02 and P < .001, respectively) and in scores on the psychosis and aggression subscales of the BEHAVE-AD rating scale (P = .005 and P < .001, respectively). Results on the Cohen-Mansfield Agitation Inventory (CMAI), which measures the frequency of symptoms, were similar: patients receiving 1 or 2 mg/d of risperidone showed significantly greater improvements than did patients receiving placebo at week 12 and at end point on the verbal, physical, and total aggression scales (P = .006 and P < .001, respectively).

The effects of risperidone on aggression were independent of improvements in psychosis, somnolence, or EPS. The incidence of EPS in patients treated with 0.5 or 1 mg/d of risperidone was not significantly different from that in patients treated with placebo, and no cases of TD were reported in either group.

Most patients continued to improve with risperidone treatment in a 1-year, open-label extension\(^{24}\) of the trial by Katz et al.\(^{13}\) A total of 330 patients elected to continue in this open-label study and were treated with 0.5 to 2 mg/d of risperidone (mean modal dose 0.96 mg/d) for an average of 230 days. Significant improvements in total scores on the BEHAVE-AD rating scale and in scores on the psychosis and aggression subscales were noted, especially among patients taking 0.75 to 1.5 mg/d of risperidone.

The efficacy and tolerability of risperidone and haloperidol in patients with BPSD were recently assessed in an international, double-blind, placebo-controlled trial.\(^{25}\) After a 1-week washout phase, 344 institutionalized patients (median age 81 years) were randomly assigned to receive placebo or flexible doses of risperidone (0.5 to 4 mg/d, mean dose 1.1 mg/d) or haloperidol (0.5 to 4 mg/d, mean dose 1.2 mg/d) for 12 weeks. Compared with those given placebo, patients given risperidone had significantly lower total and aggression cluster scores on the BEHAVE-AD rating scale at week 12 (P ≤ .05) and patients given haloperidol had significantly lower total and aggression cluster scores on the BEHAVE-AD rating scale at end point (P = .01). There were no significant changes in psychotic symptoms with treatment, which the authors attributed to the low scores on the two items of the psychosis subscale at baseline.

In general, this elderly population is prone to adverse effects, particularly EPS, cardiovascular effects, and effects on the activities of daily life. There was no difference in the incidence of EPS between the risperidone group and the placebo group (EPS were reported in 15% and 11% of the patients, respectively). The severity of EPS at end point was not significantly different between the risperidone group and the placebo group (-0.3 and -1.4, respectively); it was significantly greater with haloperidol than with risperidone (+1.6 and -0.3, respectively; increased score indicates more severe symptoms).

A comparison of the two active treatments in a post hoc analysis revealed significantly greater improvements in scores on the BEHAVE-AD aggression subscale and both total and verbal aggression scores on the CMAI among patients treated with risperidone compared with those given haloperidol.

Other adverse events occurring in 10% or more of the patients in any one group were falls,
Figure 1. Mean changes from baseline in scores on the Behavioral Pathology in Alzheimer's Disease rating scale. Significant (P = .05 to P < .0001) differences between placebo and 1 or 2 mg/d of risperidone were seen as early as weeks 2 or 3 for the total and subscale scores. Reprinted with permission from Katz IR,Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry. 1999;60:107-115.
injuries, agitation, somnolence, and purpura. Of these, only somnolence occurred in more patients receiving active treatment than in patients receiving placebo (haloperidol, 19 [18.3%]; risperidone, 14 [12.2%]; and placebo, 5 [4.4%]). There were no significant between-group differences in the occurrence of serious or severe adverse events. In addition, there was no significant difference among the three treatments on Functional Assessment Staging ratings, indicating no negative effects on daily functioning. Vital signs (blood pressure and

Figure 2. Mean changes from baseline in scores of verbal and physical aggression on the Cohen-Mansfield Agitation Inventory. Significant ($P = .03$ to $P < .001$) differences between placebo and 1 or 2 mg/d of risperidone were seen as early as weeks 2 or 3. Reprinted with permission from Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry. 1999;60:107-115.
heart rate) or electrocardiogram parameters showed no consistent changes or clinically relevant abnormalities.

**Tardive Dyskinesia**

The incidence of TD in elderly patients treated with risperidone is much lower than that in older patients treated with conventional neuroleptics. Jeste et al.\(^{28}\) have recently reported the 12-month incidence of TD among elderly patients treated with neuroleptics: 22% for patients who were neuroleptic naive at baseline, 25% for patients who had received neuroleptics for 1 to 30 days, and 37% for patients who had received neuroleptics for more than 30 days. In the study by Jeste et al.\(^{24}\) of 330 institutionalized patients with dementia, only 1 case of TD was clinically observed during the 1-year observation period. Of the 255 patients without dyskinesia at baseline, only 6 (2.4%) cases of persistent emergent TD (according to scores on the Extrapyramidal Symptom Rating Scale [ESRS]) were noted: 1 at risperidone doses of less than 0.75 mg/d; 2 at doses of 0.75 to less than 1.5 mg/d; and 4 at doses of 1.5 mg/d or more. Moreover, among the 59 patients with symptoms of dyskinesia at baseline, risperidone significantly reduced the severity of these symptoms (as measured by changes in ESRS scores) during the trial.

**Dosing Strategies for Elderly Patients With Dementia**

To lessen the risk of adverse effects, the lowest possible effective dose of risperidone should be used when treating BPDS in elderly patients. Katz et al.\(^{13}\) concluded that although both the 1-mg and the 2-mg doses of risperidone decreased aggressive and psychotic behavior in patients with dementia, the lower dose was associated with fewer adverse effects and should be considered the optimal dose for this population. In general, the doses appropriate for treating BPDS in elderly patients are lower than those recommended for treating schizophrenia\(^{27}\) or older patients.\(^{24}\) Maximum doses might be even lower for elderly patients with preexisting parkinsonism, Lewy body dementia, significant hypotension, or known EPS sensitivity to conventional neuroleptics.\(^{20}\)

Zarate et al.\(^{23}\) reported that patients whose dose of risperidone was increased slowly were less likely to experience an adverse event than were those undergoing either immediate or rapid increases in dose. One suggested titration scheme for elderly patients is a low starting dose (0.25 mg twice daily), followed by slow, incremental increases (0.25 mg every 4 days) to achieve a low mean end point dose of less than 2 mg/d.\(^{25}\) The optimal dose for most elderly patients in the two controlled studies appeared to be 1 mg/d.\(^{13,25}\) The recent availability of low-dose (0.25 and 0.5 mg) risperidone tablets and a 1-mg/mL oral solution allows for flexibility in executing this type of dosing schedule.

**CONCLUSION**

Low doses of risperidone, in the range of 0.5 to 1 mg/d, can reduce the severity and frequency of BPDS in many elderly patients. Higher doses are sometimes required to manage psychotic symptoms, such as delusional ideation and hallucinations, generally associated with a diagnosis of schizophrenia.

Low doses of risperidone are well tolerated, especially if dosing strategies tailored for elderly patients with comorbid illnesses are followed. The low incidence of EPS and TD seen with risperidone may improve compliance.

Amelioration of BPDS can improve the quality of life of patients and their caregivers and may decrease the likelihood of institutionalization. Although risperidone is more expensive than conventional neuroleptics, it can decrease other medical costs, including hospitalizations, physician visits, and emergency care, for patients with schizophrenia, savings that far outweigh the greater cost of the drug.\(^{28}\)

**REFERENCES**


