

Risperidone for the Treatment of Behavioral and Psychological Symptoms of Dementia

Larry E. Tune, M.D.

Risperidone offers physicians the unique combination of extensive, published clinical experience and a good safety profile for treating patients with dementia who have symptoms of aggression, agitation, and psychosis. Numerous open-label and, more recently, placebo-controlled trials have documented the efficacy of risperidone in the management of behavioral and psychological symptoms of dementia. These trials also show that risperidone is better tolerated than conventional neuroleptic agents. Comparatively, patients treated with risperidone experience substantially fewer side effects, including extrapyramidal symptoms, cognitive toxicity, and tardive dyskinesia.

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Until recently, the management of the behavioral and psychological symptoms of dementia (BPSD) has relied largely on an empirical combination of antidepressants, anxiolytics, neuroleptics, and other drugs. Unfortunately, the geriatric population, which constitutes the bulk of dementia sufferers, is particularly prone to the toxic effects of such medications. Consequently, the incidence of side effects has become a driving force in the prescription of these drugs. The advent of newer atypical antipsychotics for the treatment of BPSD has led to a number of clinical trials investigating their efficacy and safety. This article outlines the arguments against conventional neuroleptics and for atypical antipsychotics, risperidone in particular, in the treatment of BPSD.

THE ARGUMENT AGAINST CONVENTIONAL NEUROLEPTICS

Despite the extensive clinical use of conventional neuroleptic drugs, such as haloperidol and thioridazine, the risks associated with these drugs may outweigh potential

benefits in the treatment of BPSD. In fact, evidence that questions the role of this class of drugs in the management of dementia and agitation is increasing.

In 1990, Schneider et al.¹ performed a meta-analysis of 33 studies of neuroleptic use in elderly patients with dementia. In this analysis, conventional neuroleptics were compared with placebo and with each other. Surprisingly, these drugs were associated with an improvement of only 18% in overall symptoms when compared with placebo. Furthermore, this modest efficacy was compounded by a high incidence of side effects, including extrapyramidal symptoms (EPS), anticholinergic effects, cognitive toxicity, sedation, orthostatic hypotension, and tardive dyskinesia.

The risk of tardive dyskinesia is particularly high in elderly patients. In a study of 266 geriatric patients receiving conventional neuroleptic drugs, 26% of patients experienced tardive dyskinesia after 1 year.² This proportion increased to 52% after 2 years and 60% after 3 years (Figure 1). Finally, Tune et al.³ investigated the long-term efficacy of standard, incremental doses of haloperidol and thioridazine in 28 demented, agitated nursing home residents. At 3 months, only 2 patients were free of clinically significant drug-induced toxicity, notably EPS, and mild, drug-induced cognitive impairment.

THE ARGUMENT FOR ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics are at least as effective as conventional neuroleptic drugs in treating BPSD. Indeed, as serotonin deficiencies have been identified in the brains of patients with Alzheimer's disease at postmortem, it may be that atypical antipsychotics with serotonergic activity address the physiologic abnormalities of dementia more

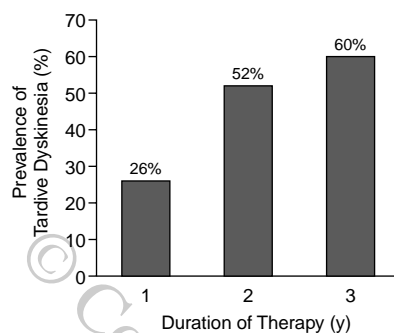
From the Division of Geriatric Psychiatry, Wesley Woods Center on Aging, Emory University School of Medicine, Atlanta, Ga.

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Reprint requests to: Larry E. Tune, M.D., Wesley Woods Geriatric Center, 1821 Clifton Rd., Atlanta, GA 30329.

Figure 1. Risk of Tardive Dyskinesia in Elderly Patients Receiving Conventional Neuroleptics (N = 266)^a



^aReprinted, with permission, from Jeste et al.²

completely than conventional neuroleptics. The differing pharmacology of these 2 groups of drugs also leads to different side effect profiles.

In general, atypical antipsychotics are much less toxic than conventional neuroleptics. Recent consensus guidelines concerning the treatment of schizophrenia give advice on the selection of antipsychotic medications to avoid side effects.⁴ This panel of experts judged that atypical antipsychotics, such as risperidone, were least likely to cause toxic effects, including EPS, tardive dyskinesia, and sexual or cognitive dysfunction (Table 1). Antipsychotic doses are generally lower in BPSD than in schizophrenia, but side effect susceptibility increases with age. These guidelines are, therefore, likely to give some indication of the incidence of side effects in elderly patients receiving antipsychotic medication for BPSD. The safety and efficacy of risperidone are also highlighted by Defilippi and Crismon,⁵ who conclude, after an extensive literature review, that it is the drug of choice for treating psychosis in patients with dementia.

However, one atypical agent, clozapine, is associated with major toxicity including agranulocytosis, seizures, sedation, orthostatic hypotension, and anticholinergic effects.⁶ Therefore, in spite of its undoubted efficacy as an antipsychotic, the drug is limited to use as a second-line agent. It retains a niche in the treatment of resistant schizophrenia and psychosis associated with Parkinson's disease or Lewy body dementia.^{7,8}

The most common side effects of atypical antipsychotics are the result of histamine (H₁) receptor and muscarinic cholinergic receptor blockade. Blockade of H₁ receptors can cause sedation and weight gain, while blockade of muscarinic cholinergic receptors may induce tachycardia, blurred vision, constipation, urinary retention, confusion, and delirium. Among the atypical antipsychotics, olanzapine has a particularly high affinity for the H₁ receptor.⁹ However, clozapine appears to be associated with the highest risk of weight gain, followed by olanzapine, then que-

Table 1. Selection of Medications to Avoid Side Effects^a

Side Effect	Drugs Least Likely to Cause the Side Effect	Drugs Most Likely to Cause the Side Effect
Sedation	Risperidone, high-potency conventional neuroleptics ^b	Clozapine, low-potency conventional neuroleptics
Weight gain	Risperidone ^b	Olanzapine, clozapine
Anticholinergic side effects	Risperidone, quetiapine, ^b high-potency conventional neuroleptics ^b	Olanzapine, low-potency conventional neuroleptics
Sexual side effects	Quetiapine, olanzapine, ^b clozapine ^b	Conventional neuroleptics
Extrapyramidal symptoms	Clozapine, quetiapine, olanzapine, risperidone ^b	Mid- and high-potency conventional neuroleptics
Cognitive side effects	Atypical antipsychotics	Low-potency conventional neuroleptics
Tardive dyskinesia	Clozapine, quetiapine, olanzapine, risperidone	Conventional neuroleptics
Cardiovascular side effects	Risperidone, high-potency conventional neuroleptics, ^b olanzapine, ^b quetiapine ^b	Low-potency conventional neuroleptics

^aAdapted, with permission, from the Expert Consensus Guideline.⁴

^bRated as a high second-line treatment by the experts.

tiapine.¹⁰ In contrast, risperidone is notable for its lack of affinity with both sets of receptors, leading to a low incidence of adverse events.

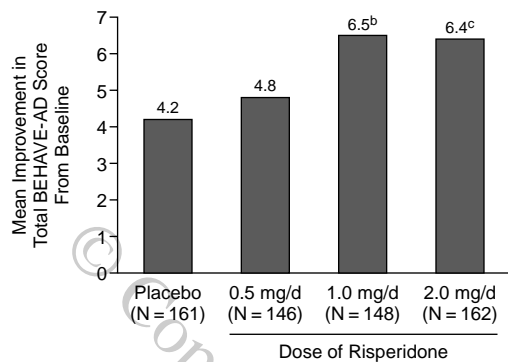
THE ARGUMENT FOR RISPERIDONE

Of all atypical antipsychotics, the greatest clinical experience has been gained with risperidone. It is now the most widely prescribed atypical agent,¹¹ with many elderly patients receiving the drug. Additionally, risperidone has a more benign side effect profile than the other antipsychotic drugs, including the atypical agents.

The efficacy and tolerability of risperidone in treating BPSD have been demonstrated by 2 double-blind, placebo-controlled clinical trials. Katz et al.¹² compared risperidone with placebo over 12 weeks in 625 patients randomly assigned to receive either risperidone, 0.5, 1, or 2 mg/day, or placebo. The mean age of the population (68% women) was 83 ± 8 years, and the mean Mini-Mental State Examination score was 6.6/30. When compared with placebo, risperidone significantly improved the total Behavioral Pathology in Alzheimer's Disease rating scale (BEHAVE-AD) score at doses of 1 mg/day (p = .002) and 2 mg/day (p = .001; Figure 2). Similar improvements were observed in the BEHAVE-AD psychosis score, for which the mean reductions from baseline were 2.5 and 2.2, respectively, for patients receiving risperidone, 1 and 2 mg/day. These improvements represented a significant advantage for risperidone, 1 mg/day (p = .005), and risperidone, 2 mg/day (p = .01), over placebo, for which mean improvement from baseline was 1.5.

Many elderly patients with dementia become aggressive. Katz and colleagues therefore evaluated the efficacy of risperidone in controlling this symptom. According to the Cohen-Mansfield Agitation Inventory (CMAI)

Figure 2. Effect of 12 Weeks of Risperidone Treatment on Total BEHAVE-AD Scores^a



^aData from Katz et al.¹² Abbreviation: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease rating scale.

^b $p = .002$ vs. placebo.

^c $p = .001$ vs. placebo.

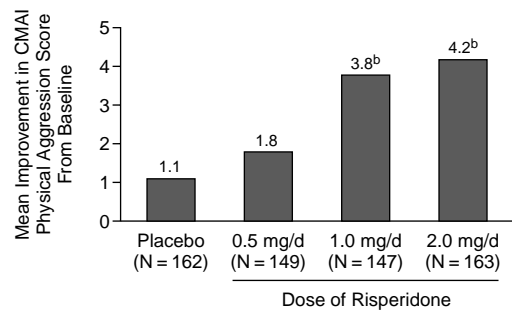
physical aggression subscale, those patients assigned risperidone at doses of 1 or 2 mg/day were significantly less aggressive than those receiving placebo ($p \leq .05$; Figure 3).

In a second, 13-week trial, De Deyn et al.¹³ compared risperidone with placebo and haloperidol for treating BPSD. A total of 344 elderly patients with dementia were randomly assigned to placebo or flexible doses of risperidone or haloperidol. At endpoint, the mean doses of risperidone and haloperidol were 1.1 and 1.2 mg/day, respectively. After 12 weeks of treatment, the authors found that, compared with placebo, risperidone was associated with a significant reduction in aggression, measured using BEHAVE-AD ($p = .002$) and CMAI ($p = .02$). A post hoc analysis also found that patients receiving risperidone were significantly less aggressive than those treated with haloperidol (BEHAVE-AD aggressiveness score, $p = .05$; CMAI total aggression score, $p = .02$).

With regard to safety, it has been shown that the incidence of EPS caused by risperidone at doses of up to 1 mg/day is not significantly greater than that caused by placebo ($p > .05$).¹² At doses of 2 mg/day, however, there is an increased incidence of EPS and sedation. At risperidone doses of up to 1 mg/day, the incidence of anticholinergic side effects such as dry mouth and urinary retention is negligible.

The risk of tardive dyskinesia is also reduced for patients receiving risperidone. In an open-label study¹⁴ of 330 elderly patients treated with risperidone (mean dose = 0.96 mg/day), the cumulative incidence of persistent emergent tardive dyskinesia was 2.6% after 1 year. Patients who presented with tardive dyskinesia at baseline experienced a significant reduction in the severity of dyskinesia after receiving risperidone, 0.75 to 1.50 mg/day, over the same period. These results contrasted sharply with those of an

Figure 3. Effect of 12 Weeks of Risperidone Treatment on CMAI Physical Aggression Subscale Scores^a



^aData from Katz et al.¹² Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.

^b $p \leq .05$ vs. placebo.

earlier study² of 266 middle-aged to elderly patients who were prescribed conventional neuroleptic agents. In this population, the cumulative incidence of tardive dyskinesia after 1 year was 26%. A further study¹⁵ directly comparing risperidone with haloperidol confirmed that risperidone was significantly less likely than haloperidol to cause tardive dyskinesia in older patients ($p < .05$).

CONCLUSION

In conclusion, risperidone is an effective drug for treatment of BPSD. It is the only atypical antipsychotic medication that has been proved, through multiple clinical trials, to reduce the symptoms of BPSD. The incidence of drug-related toxicity is also a major concern in this therapeutic area since many efficacious drugs are associated with debilitating side effects. The relatively low incidence of side effects associated with risperidone favors its use.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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