

Long-Term Safety of Risperidone

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In 2 pivotal trials comparing risperidone with placebo, the risk of adverse events was similar in both treatment groups when risperidone was given at the optimal clinical dose (1 mg/day). During 12-month, open-label extensions to these studies, the incidence of de novo tardive dyskinesia was very low. No clinically significant adverse events, changes in vital signs, or laboratory signs were observed. In summary, the safety and tolerability of risperidone in treating elderly dementia sufferers has been favorable in several clinical trials. *(J Clin Psychiatry 2001;62[suppl 21]:26–28)*

When determining the optimal period of treatment with antipsychotic agents for patients suffering from the behavioral and psychological symptoms of dementia (BPSD), physicians must consider a number of factors. Uppermost is the potential incidence of side effects, since elderly patients with dementia are particularly susceptible to drug-related adverse events. The risk of adverse events increases with length of treatment, so long-term safety is an important facet of any agent for BPSD. This article reviews the efficacy and tolerability of long-term treatment with the new antipsychotic agent risperidone and the safety of its combination with other medications.

FOR HOW LONG SHOULD BPSD BE TREATED?

When considering pharmacotherapy to manage BPSD, a careful balance must be struck between the benefits of symptom control and the inherent risks associated with most psychotropic agents in the elderly. Elderly patients with dementia are highly susceptible to side effects from antipsychotic medication, and this risk probably increases with the duration of treatment. The length of time a patient should be treated with antipsychotic drugs following alleviation of BPSD symptoms is therefore a pertinent clinical question.

Consider a patient suffering from BPSD. Over several weeks or months of antipsychotic medication, symptoms have ameliorated or even disappeared. Should maintenance therapy be prolonged, or is it now appropriate to stop pharmacologic therapy? No reliable predictors of

symptom relapse following the discontinuation of medication have yet been identified, so in deciding their course of action physicians must take a number of factors into account. For example, BPSD tend to fluctuate spontaneously, gradually improving or worsening over a period of time.^{1,2} In addition, different symptoms appear as the condition progresses,³ and agent-induced side effects can, in fact, resemble certain aspects of BPSD. Furthermore, there may be discrepancies or inaccuracies in the reporting of symptoms by cognitively impaired patients, frustrated or exhausted caregivers, and/or busy members of staff. Finally, and perhaps most importantly, the decision is dictated by the anticipated incidence of adverse events, although this in itself can be difficult to assess.

PREDICTING AND PREVENTING SIDE EFFECTS

Some of the adverse effects of antipsychotic drugs are predicted by their receptor binding profiles (Table 1). For example, drugs with strong dopaminergic binding affinities, such as haloperidol, are most likely to cause extrapyramidal side effects (EPS). Antimuscarinic properties, such as those seen with clozapine, result in anticholinergic side effects, and drugs that antagonize histamine receptors (e.g., chlorpromazine) can be sedative in nature, perhaps even causing cognitive impairment. In general, conventional neuroleptics have poorer side effect profiles than atypical antipsychotics.⁶ Patients receiving low-potency conventional neuroleptics are at higher risk of experiencing sedation, orthostatic hypotension, and transaminase elevation. Arrhythmogenic effects are not a major issue in treatment with neuroleptics; however, thioridazine, which is still widely used, and, possibly, the novel antipsychotic ziprasidone, may prolong the QT interval. Acquired QT prolongation can predispose patients to extremely rare but fatal ventricular tachyarrhythmias. However, it should be noted that no direct link between antipsychotic drugs, QT interval prolongation, arrhythmias, and death has been proved.

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Presented at the symposium "Restoring Harmony—Adding Life to Years," which was held June 16–17, 2000, in Seville, Spain, and supported by an unrestricted educational grant by Janssen Cilag and Organon.

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Table 1. Receptor-Binding Affinities as Predictors of Side Effects of Antipsychotic Drugs^a

Drug	Stronger Affinity	Weaker Affinity
Haloperidol	D ₂ , D ₁ , α_1	5-HT _{2A} , M ₁ , H ₁
Clozapine	M ₁ , H ₁ , α_1	5-HT _{2A} , D ₁ , D ₂
Risperidone	5-HT _{2A} , α_1 , D ₂	D ₁ , H ₁ , M ₁
Olanzapine	M ₁ , 5-HT _{2A} , H ₁	D ₂ , α_1 , D ₁

^aData from Bymaster et al.⁴ and Schotte et al.⁵

Abbreviations: 5-HT_{2A} = serotonin receptor, α_1 = α_1 adrenoceptor, D = dopamine receptors, H₁ = histamine receptor, M₁ = muscarinic receptor.

In addition, it appears that treatment of demented patients with conventional neuroleptics may hasten cognitive decline.⁷ A large number of open-label studies suggest that conventional neuroleptics might impair cognitive performance.⁸ Conversely, atypical antipsychotics do not appear to affect cognitive function. For example, in their double-blind, placebo-controlled studies, both De Deyn et al.⁹ and Katz et al.¹⁰ showed that risperidone was not associated with impairment in cognitive function.

If the side effect profiles of antipsychotic agents are determined by their affinity for various neurotransmitter receptors, then the manifestation of such side effects should be dependent upon receptor binding. For example, a positron emission tomography (PET) study examining the use of haloperidol in young schizophrenic patients showed that dopamine receptors are 70% to 80% saturated at 2.5-mg/day doses (Figure 1).¹¹ Further increases in haloperidol dose resulted in akathisia and EPS, but no increase in saturation. Similarly, it has been shown that the optimal dose of risperidone for treating BPSD is 0.5 to 1.5 mg/day. Increasing the dose further does not significantly increase either dopamine or serotonin receptor saturation.¹²

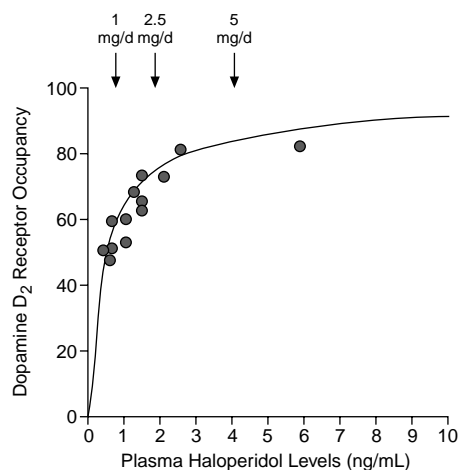
Increasing the dose of antipsychotic medication above optimal levels results, therefore, in an increased level of side effects with little benefit in terms of symptom control.

RISPERIDONE: SUSTAINED EFFICACY AND TOLERABILITY

Risperidone has a weak affinity for both histamine and muscarinic receptors (see Table 1). This, combined with a moderate affinity for dopamine receptors, gives the drug a relatively benign side effect profile. In comparison, clozapine and olanzapine are more potent antagonists of histamine receptors than risperidone and may cause sedation or weight gain.⁶ Similarly, both olanzapine and clozapine are also more potent blockers of muscarinic receptors than risperidone.⁶

Two large-scale, double-blind trials^{9,10} have demonstrated the efficacy of risperidone for treating aggression, agitation, and psychotic symptoms in dementia. Over 12 weeks, the incidence of EPS among patients receiving risperidone (0.5–1 mg/day) was statistically equivalent to

Figure 1. Dopamine D₂ Receptor Occupancy by Haloperidol^a



^aReprinted, with permission, from Kapur et al.¹¹

that of those receiving placebo. Only at doses of 2 mg/day did EPS become significant. Both trials were subsequently extended over 12 months (open-label) in order to assess the long-term effects of risperidone therapy.

SAFETY OF RISPERIDONE IN COMBINATION WITH ACETYLCHOLINESTERASE INHIBITORS

Many patients with Alzheimer's disease are now prescribed an acetylcholinesterase inhibitor, e.g., donepezil or rivastigmine, in conjunction with their antipsychotic medication.

A study from the United States has assessed the pharmacokinetic profiles of risperidone and donepezil when administered concurrently (J. E. Mintzer, written communication, June 2000). This open-label, randomized, crossover trial involved 24 young, healthy, male volunteers. Each volunteer received, risperidone, 0.5 mg b.d.; donepezil, 5 mg q.d.; or a combined regimen for 14-day intervals. During the trial, the most frequently reported adverse event was headache, followed by somnolence, nervousness, and dizziness. The incidence of these events did not vary significantly between the 3 dosage regimens. The combination of risperidone and donepezil had no effect on the pharmacokinetics of either drug.

CONCLUSIONS

Risperidone is an effective agent for the treatment of BPSD with good tolerability. It does not impair cognitive function and shows no evidence of anticholinergic side effects, and the incidence of EPS is equivalent to that seen with placebo at effective doses. Furthermore, risperidone is not overly sedative, is associated with a very low risk of

tardive dyskinesia, and does not interact with acetylcholinesterase inhibitors when used in combination.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), donepezil (Aricept), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), rivastigmine (Exelon), ziprasidone (Geodon).

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