

# Psychopharmacology of Atypical Antipsychotics and Clinical Outcomes in Elderly Patients

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The differential effects of receptor blockade on the clinical efficacy and safety of atypical antipsychotics are reviewed. Studies of both clozapine and risperidone in geriatric patients have been published. Clozapine appears to have a greater side effect burden than risperidone. No studies of olanzapine or quetiapine in the elderly have been published. In a recent double-blind study, 625 patients with Alzheimer's disease, vascular dementia, or mixed dementia were randomly assigned to receive risperidone (0.5, 1, or 2 mg/day) or placebo for 12 weeks. Risperidone was found to be significantly more effective than placebo in reducing psychotic symptoms and the severity and frequency of aggressiveness. The optimal dose of risperidone in terms of both efficacy and safety was 1 mg/day. In an open-label trial, 103 elderly patients with a diagnosis of schizophrenia or schizoaffective disorder received risperidone for 12 weeks. The mean risperidone dose was 2.4 mg/day. Clinical improvement (20% reduction in Positive and Negative Syndrome Scale [PANSS] total scores) was seen in 50%; the severity of positive and negative symptoms (PANSS positive and negative scores) was significantly improved, and the frequency of extrapyramidal symptoms was significantly reduced. It is concluded that risperidone is efficacious and safe in the treatment of elderly patients with dementia or psychoses.

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The elderly constitute a large and growing proportion of the American population and present special problems in pharmacotherapy arising from age-related pharmacokinetic and pharmacodynamic alterations. Furthermore, because many elderly patients have manifold medical conditions, they are likely to be on multiple-drug regimens, increasing their susceptibility to drug-drug interactions and adverse effects.

Geriatric subpopulations of particular interest to psychiatrists are aging schizophrenics and patients with dementia, both of whom are often treated with antipsychotic agents. Use of the conventional neuroleptic agents has been associated with adverse events including extrapyramidal symptoms (EPS), tardive dyskinesia, and anticholinergic effects.<sup>1</sup> Concerns about these effects have spurred interest in use of the newer atypical antipsychotic agents, of which clozapine and risperidone have been the most extensively studied. Other agents in this category include olanzapine and quetiapine.

The atypical antipsychotic medications differ in several ways from the conventional medications. Although there is a paucity of clinical data on the use of these atypical antipsychotic drugs in the elderly, studies of clozapine and risperidone have demonstrated their efficacy in treating both positive and negative psychiatric symptoms. In addition, they cause no or minimal EPS and carry a low risk of tardive dyskinesia or dystonia. Conventional antipsychotic agents such as haloperidol and chlorpromazine, on the other hand, effectively treat the positive symptoms of schizophrenia but have little or no effect on negative symptoms, including blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, and lack of spontaneity.

Differences in efficacy, safety, and tolerability between the conventional and atypical antipsychotic agents are influenced by their receptor binding profiles. Most of the older drugs block the dopamine receptors located in the brain's mesolimbic, striatal, and mesocortical systems, whereas the newer agents are more selective. These newer drugs, called serotonin-dopamine antagonists, have a higher binding affinity for serotonin receptors than for dopamine receptors.

## SPECIFIC NEUROTRANSMITTER RECEPTORS

The role of specific neurotransmitters in psychosis has been complicated by the identification of 5 dopamine receptor subtypes and 14 serotonin receptor subtypes.

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Table 1. Receptor Binding Affinity<sup>a</sup> of Antipsychotic Agents

Agent	Dopamine		Serotonin		$\alpha$ -Adrenergic $\alpha_1$	Histamine H <sub>1</sub>	Muscarinic M <sub>1</sub>
	D <sub>1</sub>	D <sub>2</sub>	5-HT <sub>1A</sub>	5-HT <sub>2A</sub>			
Haloperidol	++++	++++	+	+++	+++	++	++
Clozapine	+++	+++	++	++++	++++	++++	++++
Risperidone	+++	++++	++	++++	++++	+++	0
Olanzapine	++++	++++	+	++++	++++	++++	++++
Quetiapine	+	+++	+	+++	++++	++++	+++

<sup>a</sup>Authors' judgment based on published K<sub>i</sub> and IC<sub>50</sub> values: ++++ (high) = K<sub>i</sub> ≤ 40 nM; +++ (moderate) = K<sub>i</sub> 50–250 nM; ++ (weak) = K<sub>i</sub> 450–1000 nM; + (very weak) = > 1000 nM; 0 (none) = < 50% binding inhibition at 10,000 nM. Sources: Pickar,<sup>2</sup> Schotte et al.,<sup>3</sup> and Bymaster et al.<sup>4</sup>

Agents that bind to serotonin 5-HT<sub>2</sub> (5-hydroxytryptamine) receptors are associated with fewer side effects than those that bind only to dopamine receptors. Binding affinities for  $\alpha$ -adrenergic, histaminic, and muscarinic receptors also are important, particularly as they affect a drug's tolerability. For example, the elderly are particularly susceptible to postural hypotension associated with  $\alpha$ -adrenergic blockade, sedation or drowsiness associated with histaminic or  $\alpha$ -adrenergic blockade, and the variety of unwanted anticholinergic effects associated with muscarinic blockade, such as dry mouth, blurred vision, constipation, sedation, and confusion.

The relative receptor affinities of antipsychotic compounds have been investigated.<sup>2-4</sup> A compound that occupies only the dopamine D<sub>1</sub> receptor has no antipsychotic effect; D<sub>2</sub> blockade is necessary. At therapeutic doses, haloperidol occupies more than 70% of D<sub>2</sub> receptors and carries a high risk of EPS. In contrast, clozapine occupies 20% to 60% of dopamine D<sub>1</sub> and D<sub>2</sub> receptors and more than 70% of 5-HT<sub>2</sub> receptors. Risperidone has no affinity for dopamine D<sub>1</sub> receptors but, at clinically effective doses, occupies more than 70% of dopamine D<sub>2</sub> and serotonin 5-HT<sub>2</sub> receptors. With respect to 5-HT<sub>2</sub>:D<sub>2</sub> ratios, clozapine has the highest ratio (about 20), with risperidone about 10.7 and olanzapine about 2.57.

The antipsychotic effect of monoamine receptor occupancy for 5 drugs has been determined by positron emission tomography.<sup>5</sup> SCH 39166, which blocks only D<sub>1</sub> receptors, was developed because animal models predicted that it would have antipsychotic effects. It was found to have none, whereas haloperidol, remoxipride, clozapine, and risperidone, which block D<sub>2</sub> receptors, do have antipsychotic effects. Clozapine has a strong D<sub>4</sub> blockade (similar to a D<sub>2</sub> blockade). Compounds that block only D<sub>4</sub> can be good antipsychotic agents. With D<sub>1</sub> and D<sub>5</sub>, an agonist is required, and with D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub>, an antagonist is required. Compounds that have more D<sub>1</sub> blockade may cause negative symptoms in schizophrenic patients.

Clozapine and olanzapine block histaminic and muscarinic receptors to a greater extent than risperidone does (Table 1), and this blockade is relevant to adverse effects in geriatric patients. Agents with a high affinity for muscarinic receptors often cause the distressing anticholinergic side effects noted above and may increase confusion in

cognitively impaired elderly patients. Agents with a high affinity for muscarinic receptors should not be used in elderly patients, especially those with dementia. However, the degree of affinity for receptors may not always correlate with the clinical symptoms. The only benefit of the muscarinic blockade that has been postulated is that it

may mitigate some of the EPS effects by blocking muscarinic agonists and muscarinic receptors. Blockade of  $\alpha_2$ -adrenergic receptors causes priapism and inhibits the antihypertensive effects of clonidine, methyl dopa, guanabenz, and guanfacine. Blockade of  $\alpha_1$  receptors may increase norepinephrine activity, which offers no benefit beyond questionable antipsychotic properties.

The development of EPS is attributed to the blockade of D<sub>2</sub> receptors in the dorsal striatum, a region of the basal ganglia that integrates sensorimotor control. The 5-HT<sub>2</sub> blockade counteracts the inhibition of dopamine release. Thus, in the presence of 5-HT<sub>2</sub> blockade and D<sub>2</sub> blockade, EPS are reduced.

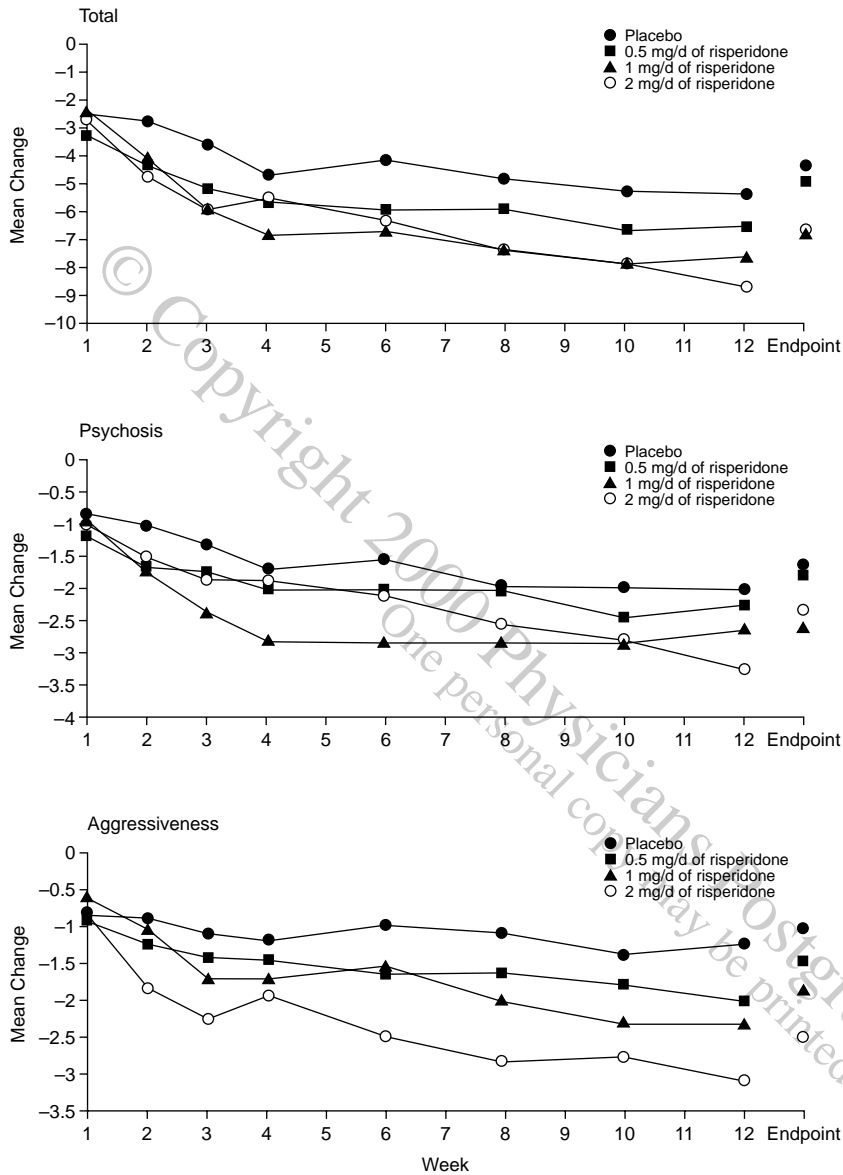
#### ATYPICAL ANTIPSYCHOTICS IN GERIATRIC PATIENTS

Several open-label studies of risperidone<sup>6,7</sup> and clozapine<sup>8-11</sup> in geriatric patients have been published. The study patients included those with early or late onset of schizophrenia or psychotic depression. Although both agents are effective for treatment of dementia with psychosis, dementia with agitation, delirium, and other psychoses, clozapine has a greater side effect burden than does risperidone. Compared with clozapine, risperidone causes less sedation and EPS and has virtually no anticholinergic activity. Furthermore, clozapine, but not risperidone, is associated with a risk of agranulocytosis.

Other atypical antipsychotic agents approved by the FDA include olanzapine and quetiapine, but no studies of their use in geriatric patients have been published.

#### Efficacy and Safety of Risperidone in Elderly Patients

Risperidone has been shown to be an effective antipsychotic agent with a reduced rate of EPS and a side effect profile that suggests its usefulness for older patients. It does not reduce the seizure threshold. It does not block histaminic receptors, which accounts in large measure for its lack of sedation. It is not an anticholinergic, which removes any risk of symptoms such as constipation, urinary retention, visual difficulties, and dry mouth. It does not cause cardiovascular and laboratory abnormalities, and when started at low doses and increased slowly, it causes

Figure 1. Mean Changes From Baseline in BEHAVE-AD Scores<sup>a</sup>

<sup>a</sup>From Katz et al.,<sup>12</sup> with permission. Significant ( $p = .05$  to  $p < .0001$ ) differences between placebo and 1 mg/day or 2 mg/day of risperidone were seen as early as weeks 2 or 3 on the total and subscale scores. A lower score indicates less severe symptoms.

little orthostatic hypotension. Because of the apparent benefits of risperidone for elderly patients, studies of risperidone in the 2 important groups of elderly patients, patients with the noncognitive symptoms of dementia and older patients with schizophrenia or schizoaffective disorder, were conducted.

**Elderly patients with dementia.** A large, randomized, double-blind trial of patients with dementia has recently been completed.<sup>12</sup> The subjects were 625 patients with a diagnosis of Alzheimer's disease, vascular dementia, or mixed dementia, all of whom were in a hospital or a nurs-

ing home. This was a 12-week multicenter comparison of risperidone at daily doses of 0.5 mg, 1 mg, and 2 mg versus placebo.

The primary measure of efficacy was the Behavior Pathology in Alzheimer's Disease Rating Scale<sup>13</sup> (BEHAVE-AD). BEHAVE-AD is a 25-item questionnaire about the severity of psychopathology in demented patients. Twelve of the questions pertain to psychosis, including 7 relating to delusions that are particularly prevalent in the elderly, such as "my house is not a home" or "my caretaker is an imposter." Five questions apply to hallucinations and 3 to aggression, an important symptom in the elderly that often leads to institutionalization. Other questions relate to affective disturbances, anxiety, and motor disturbances such as wandering.

The average age of the study population was 83 years. Most were women, as would be expected by the Life Table Data in the United States population, and most were white. Most of the patients had Alzheimer's disease, with a frequency ranging from 67% to 80%. There were no significant between-group differences in demographics or diagnosis. The average age at onset of dementia was about 75 years. The average duration of stay in the institution was 12 to 13 years. The patients were severely demented, as would be expected from the fact that they were institutionalized. More than 90% of the patients had Functional Assessment Staging<sup>14</sup> (FAST) scores of 6 or greater. A score of 6 on the FAST not only indicates a significant cognitive deficit but also implies significant impairments in self-care.

Treatment response, defined as a  $\geq 50\%$  reduction in BEHAVE-AD total scores, was seen in significantly more patients receiving 1 mg/day (45%) and 2 mg/day (50%) of risperidone than placebo (33%). On the BEHAVE-AD total score and the psychosis and aggressiveness subscales, improvements were significantly greater in patients receiving 1 or 2 mg/day of risperidone than placebo, with

Table 2. Adverse Events Reported by at Least 10% of Patients in Any Treatment Group<sup>a</sup>

Adverse Event	Placebo (N = 163) %	Risperidone		
		0.5 mg/day (N = 149) %	1 mg/day (N = 148) %	2 mg/day (N = 165) %
Injury	37.4	32.9	28.4	31.5
Somnolence	8.0	10.1	16.9	27.9
Fall	20.2	16.1	12.8	24.8
Extrapyramidal disorder <sup>b</sup>	7.4	6.7	12.8	21.2
Urinary tract infection	12.9	16.1	12.8	21.2
Peripheral edema	5.5	16.1	12.8	18.2
Purpura	11.7	16.8	12.2	10.3
Fever	7.4	10.1	7.4	14.5
Pain	8.0	8.1	2.7	10.3
Coughing	8.0	10.7	5.4	8.5
Agitation	10.4	7.4	5.4	8.5
Rhinitis	5.5	4.7	6.1	10.3
Upper respiratory tract infection	3.7	10.1	7.4	5.5

<sup>a</sup>Adapted from Katz et al.,<sup>12</sup> with permission.

<sup>b</sup>Includes hyperkinesia, hypertonia, tremor, dystonia, involuntary muscle contractions, abnormal gait, hypokinesia, oculogyric crisis, ataxia, hyporeflexia, choreoathetosis, aggravated parkinsonism, and tongue paralysis.

significant improvements as early as week 2 (Figure 1). Significant improvements were seen on all of the paranoid/delusional ideation items of the psychosis subscale. Ratings of hallucinations were low at baseline in all groups, with no significant differences between groups in change scores. All 3 risperidone groups also had significantly better scores than did placebo patients on the BEHAVE-AD aggressiveness subscale at week 12; risperidone at 1 and 2 mg/day was superior to placebo at endpoint. While improvements in the risperidone-treated patients were noted on the other subscales of the BEHAVE-AD, the differences versus placebo were not significant.

One dose-related symptom observed in the risperidone groups that could have affected efficacy was somnolence. However, a reanalysis of all of the data excluding patients with somnolence did not change the results.

In this highly vulnerable population, there was no clustering of serious adverse events or deaths in the risperidone groups, and the incidence of serious adverse events and deaths did not differ significantly between the risperidone and placebo groups. No dose-related trends for any of the adverse events were apparent except somnolence, EPS, and peripheral edema (Table 2). Because of the higher frequencies of somnolence and EPS at higher risperidone doses, we recommend 1 mg as the optimal dose in dementia.

Cardiovascular events were equally distributed across the treatment groups. There was minimal QTc prolongation in this particularly vulnerable patient population. At the target dose of 1 mg/day, there was a 1.75 msec prolongation at endpoint, which is indistinguishable from placebo

(1.7 msec prolongation in the placebo group). A more precise estimate of any risks associated with QTc prolongation is the proportion of patients who had a QTc interval < 450 msec at baseline and a QTc interval > 450 msec during the trial; this was seen in 17% of the placebo group and in 17%, 15%, and 16% of the 3 risperidone groups.

**Elderly patients with schizophrenia or schizoaffective disorder.** One hundred three elderly patients (52 men and 51 women) with a diagnosis of schizophrenia (N = 77) or schizoaffective disorder (N = 26) were enrolled in a 12-week, open-label trial of risperidone.<sup>15</sup> Their mean age was 71 years, age at first psychiatric diagnosis was 35, and the mean duration of treatment before entry into the study was 72 days. All patients were hospitalized in either a nursing home or an inpatient facility.

Patients received 0.5 mg of risperidone twice daily on day 1 and were allowed to increase the dose in increments of 0.5 mg twice daily to a maximum dose of 3 mg/day. The average dose during the trial was 2.4 mg/day, which is probably representative of the doses that should be used in older psychotic patients. The key outcome measures were the Positive and Negative Syndrome Scale<sup>16</sup> (PANSS), the Clinical Global Impressions (CGI) scale,<sup>17</sup> and the Extrapyramidal Symptoms Rating Scale<sup>18</sup> (ESRS). These assessments were performed at weeks 1, 2, 4, 6, 8, 10, and 12.

Clinical improvement was defined as a reduction of 20% or more in the total PANSS scores. A second definition was a 20% reduction in total PANSS and a rating of at least minimally improved on the CGI scale. Using the definition of the reduction in the PANSS, 50% of all patients improved. Improvement was no greater in patients who received more than 3 mg/day than in those who received less than 3 mg/day. Using the more stringent definition, 45% of all patients improved. There was an advantage insofar as 48% of patients receiving  $\leq$  3 mg/day of risperidone improved compared with 36% of patients who received > 3 mg/day. Since this was a flexible-dose trial, doses were higher for patients who tolerated the medication and who did not respond to lower doses. However, we believe that doses > 3 mg are not necessary.

In the entire group, the change in total PANSS scores averaged 11 points, with an almost 4-point improvement in positive symptoms and a 22-point improvement in negative symptoms. These changes were statistically significant. Eleven percent of the patients were very much improved on the CGI, and 62% improved at least minimally. Only 12% of patients had worsened between baseline and the endpoint.

Equally important as the efficacy of risperidone was its reduced frequency of EPS. In this population of patients, all the endpoint scores on the ESRS were improved from baseline scores. Improvements were seen on the questionnaire; the total score of parkinsonism, dystonia, and dyskinesia; the global rating of dyskinesia; and the global rating of parkinsonism.

The most common and clinically relevant adverse event reported was dizziness, an important side effect in elderly schizophrenic patients, because the propensity for falling could lead to fractures in patients with reduced bone mass. Dizziness, experienced by 22% of patients, was probably due to a faster than optimal dose-increase schedule. Increasing the doses more gradually should reduce the dizziness. Three patients had falls that were attributable to either dizziness or orthostatic hypotension.

Changes in the electrocardiogram are important in this population of older patients; notably, QTc prolongation is particularly relevant in older patients. The average QTc was not prolonged at week 6, week 12, and endpoint. Consistent with experience in other clinical trials with risperidone, there was no pattern of laboratory abnormalities.

In summary, in this small open study, risperidone significantly improved psychotic symptoms in elderly patients. Significant reductions in the PANSS scores were observed during the first week of treatment and were maintained throughout the 12-week trial. There was no advantage in doses higher than 3 mg. Extrapyramidal symptoms were reduced on risperidone compared with other medication; risperidone was well tolerated by this cohort of patients.

### CONCLUSION

These data show that risperidone not only is effective in treating psychotic and aggressive symptoms in patients with dementia and psychotic symptoms in elderly patients with schizophrenia, but is also safe for use in these populations. The clinical profile predicted by the pharmacologic profile was borne out in actual clinical practice. We therefore consider risperidone to be an attractive compound for use in elderly patients with dementia and schizophrenia or schizoaffective disorder.

*Drug names:* chlorpromazine (Thorazine and others), clonidine (Catapres), clozapine (Clozaril), guanabenz (Wytensin and others), guanfacine (Tenex and others), haloperidol (Haldol and others), methyl-dopa (Aldomet and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside Food and Drug Administration–approved labeling.

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