Optimal Dosing With Risperidone: Updated Recommendations

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Background: Drug dosages utilized during controlled clinical trials are not always optimal for patients encountered in day-to-day practice. The original trials of risperidone, a novel antipsychotic, suggested that an initial target dose of 6 mg/day was appropriate, but these trials were necessarily conducted among patients who were chronically impaired, hospitalized, and often partly drug resistant.

Data Sources: Relevant data relating to the dosage of risperidone identified through an online (MEDLINE) search using the keywords *risperidone*, *schizophrenia*, *schizoaffective disorder*, *dementia*, *bipolar disorder*, and *dose* were supplemented by a review of international and U.S. Congress abstracts in which the dose of risperidone was specifically described.

Conclusion: On the basis of naturalistic studies, clinical audit, phase 4 trials, positron emission tomography data, and 5 years of clinical experience, the currently recommended target dose of risperidone is 4 mg/day for most patients, with less-rapid titration than previously recommended. Moreover, a lower dose than this and slower titration may be appropriate for elderly patients, young patients, and first-episode patients.

(J Clin Psychiatry 2001;62:282–289)

Received Aug. 5, 2000; accepted Nov. 15, 2000. From the Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada.

Supported by an unrestricted grant from Janssen-Cilag Pharmaceuticals, Beerse, Belgium, and NV Organon, Oss, the Netherlands. The author is grateful to these sources for assisting with database searches to enable identification of appropriate references.

Financial disclosure: Dr. Williams has received grants from Janssen-Ortho, Inc., Eli Lilly Canada, AstraZeneca, Pfizer, Hoechst Marion Roussel (Aventis), Novartis, and Bristol-Myers Squibb and has received honoraria from Janssen, Eli Lilly, and Pfizer.

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Dosing is a critical issue in the administration of antipsychotic drugs, in which both efficacy and tolerability are concerned. In the case of the newer antipsychotics, as in that of the conventional agents, dosages applied to highly selected trial populations are not always optimal for groups of patients encountered in day-to-day practice. Risperidone, a benzisoxazole derivative, is a novel atypical antipsychotic drug with antagonistic action at both serotonin-2 ($5\text{-}HT_2$) and dopamine D_2 receptors. Risperidone has proved effective in the treatment both of the positive and negative symptoms of schizophrenia and has a low potential for inducing extrapyramidal symptoms (EPS).[1,2] The early multicenter trials of risperidone in schizophrenia suggested that 4 to 8 mg/day was the optimal dose range for maximal efficacy and minimal induction of EPS. On this basis, dosing recommendations proposed a target dose of 6 mg dailytitrated in 2-mg increments over 3 days, with subsequent adjustment of the dose to 4 or 8 mg/day depending on side effects or lack of efficacy.

However, the subjects of these early trials were generally chronic patients who had experienced many years of illness and high-dose medication. Furthermore, the original studies were of short duration, typically 6 to 8 weeks, and they examined doses of risperidone between 2 and 16 mg/daya range that was in line with dose-ranging estimates at that time. Subsequent clinical experience with risperidone has suggested that, in the more heterogeneous population encountered in day-to-day practice, the original recommendations of doses over 6 mg/day are not always appropriate. Clinicians have noted that the dose titration was often too rapid and/or the target dose too high, and that this caused some patients to experience unwanted side effects that could have been avoided with a more appropriate dose regimen. This article examines the evidence to justify dosage revisions based on data concerning more recent use of risperidone in normal clinical practice situations.

Relevant data relating to the dosage of risperidone identified through an online (MEDLINE) search using the keywords *risperidone*, *schizophrenia*, *schizoaffective disorder*, *dementia*, *bipolar disorder*, and *dose* were supplemented by a review of international and U.S. Congress abstracts in which the dose of risperidone was specifically described.

EARLY CLINICAL TRIALS

Data from clinical trials in schizophrenia during the early 1990s indicated that the optimal daily dose of risperidone for most patients was 6 to 8 mg.[1,2] These doses were as effective as higher doses in controlling psychosis, with no greater incidence of EPS than in patients receiving placebo. All patients in these early trials were hospitalized with an acute exacerbation of chronic schizophrenia. In the first published trial in Canada in 1993,[1] the 135 patients had an average of 7 previous hospitalizations, and, in another trial reported in 1994 from the United States,[2] the 388 patients enrolled were described as "a group of chronically impaired men and women who had been hospitalized an average of 9 times previously and who had been in the hospital for an average of 29 weeks before study entry."(p828) These patients are not typical of the general population of people who suffer from schizophrenia and who are generally treated in the community.

META-ANALYSIS OF OTHER CLINICAL TRIAL DATA

By 1999, Lemmens et al.[3] were able to analyze data from 27 double-blind and open-label risperidone trials involving 3298 patients with chronic schizophrenia who were treated with risperidone. Their meta-analysis showed that there was generally no greater efficacy of risperidone with doses over 4 mg/dayThis analysis also indicated that factors associated with greater EPS severity included a risperidone dose in excess of 8 mg/dayThese authors concluded that 4 mg/day is an appropriate initial target dose for most patients with recurrent acute episodes of schizophrenia. Higher doses, they suggested, might be appropriate for a few patients with chronic illness, and lower doses were considered to be usually appropriate for patients with a first psychotic episode or for elderly patients.

Kasper[4] examined data derived from clinical trials and market research with risperidone to help clinicians determine the most clinically appropriate dose with demonstrated efficacy and minimal side effects. Results of clinical trials consistently suggested 4 to 6 mg/day to be an appropriate dose range for patients with chronic schizophrenia. Lower doses were considered appropriate for patients such as the elderly and those experiencing a first schizophrenic episode. Postmarketing data suggested, in Kasper's view, that doses higher than 6 mg/day were associated with more EPS without a substantial increase in efficacy and that such doses are not optimal for most patients.

NATURALISTIC STUDIES

Because of necessarily rigid selection criteria, initial clinical trials of new compounds cannot be used in the diversity of patients or therapeutic situations commonly encountered in clinical practice. Naturalistic studies, however, have the advantage of providing data on heterogeneous patient groups in more realistic settings. Data from such studies reflect the use of a drug in day-to-day clinical practice.[5] Outcomes of 11 naturalistic studies involving risperidone are summarized here. Eight of these were clinical audit-type studies, and 3 were postmarketing surveillance studies.

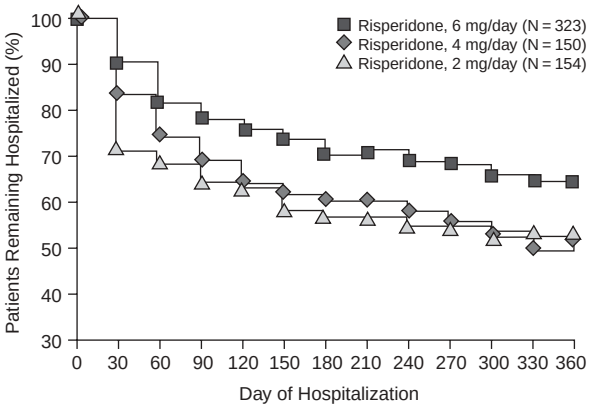
In 1997, Albus et al.[5] reported a postmarketing surveillance study of risperidone in the treatment of 886 patients with chronic schizophrenia. The mean daily dose at 6 months was 4.8 mg. Patients who had previously received neuroleptics received higher doses of risperidone than those with no previous neuroleptic treatment.

In a separate postmarketing surveillance study reported in the same year, Jeste et al.[6] evaluated the efficacy and safety of risperidone in a heterogeneous population of 945 patients with schizophrenia, of which 251 patients (27%) were described as treatment resistant. The mean dose of risperidone at endpoint (10 weeks) was 5.9 mg/day. Significant improvement in symptoms was observed, with comparable results in treatment-resistant and non–treatment-resistant patients. Risperidone was generally well tolerated, and the severity of EPS was significantly reduced at endpoint.

Love et al.[7] reviewed the records of 1056 patients receiving risperidone in Maryland inpatient psychiatric facilities from 1994 to 1997. The mean daily dose for those initiated on risperidone treatment declined significantly from 6.4 mg/day in 1994 to 5.1 mg/day in 1996. Patients who were discharged were treated with significantly lower doses than those who remained as inpatients (e.g., 4.3 mg/day vs. 5.6 mg/day in 1996) (Figure 1).

Chouinard et al.[8] reported a phase 4 open-label flexible-dose study in 1998 that assessed the efficacy and safety of risperidone in 330 outpatients with schizophrenia. Risper-

Figure 1. Hospital Discharge Rate by Dose of Risperidone[a]



[a]Adapted from Love et al.,[7] with permission. 2 mg vs. 6 mg, p = .0009; 4 mg vs. 2 mg, p = .005; 6 mg vs. 4 mg, p = .65.

idone was found to be superior in efficacy to the neuroleptics that the patients had previously been taking and was found to produce fewer EPS. Although the mean final titrated dose was 6.1 mg daily, the final titrated dose was 4 mg daily in 23% of patients, suggesting, in the authors' view, that a target dose of 6 mg/day was higher than necessary.

Computerized pharmacy data on 1283 patients with schizophrenia (65%) or schizoaffective disorder (35%) who had been treated with risperidone were reported by Luchins et al.[9] in 1998. Their findings suggested that the recommended dose schedule should be altered to one that includes a less-rapid titration (over 6 days to a week) and that the dose increments should consist of 0.5 to 2 mg/day. In their study, a maximum rate of increase of 0.5 to 2 mg/day was associated with lower rates of discontinuation of risperidone, whereas rates of dose increases of greater than 2 mg/day were associated with higher rates of discontinuation.

Also in 1998, Procyshyn and Zerjav[10] reported a nonrandomized retrospective chart review of 60 consecutive patients presenting with psychotic symptoms on inpatient wards, 30 of whom were given risperidone as their first new drug after reassessment. Patients were admitted between November 1996 and September 1997, and data were collected for up to 120 days. The mean ± SD dosage of risperidone was 4.9 ± 2.6 mg/day for responders and 4.3 ± 1.9 mg/day at discharge. The rate of EPS for responders was 11.0%.

In 1999, Chengappa et al.[11] reported outcome data for 142 patients 2 years after initiation of treatment with risperidone. The majority of patients had a diagnosis of schizophrenia (57%) or schizoaffective disorder (22%). Dementia and other organic conditions, bipolar disorder, and other psychiatric disorders comprised the remainder. In that study, the modal maximum daily dose of risperidone was 4.1 mg in patients discharged on risperidone treatment and 7.5 mg in patients remaining in hospital.

In the same year, Kelly et al.[12] reported on 309 patient records from Maryland state psychiatric facilities in the first year of use of risperidone (after a 6-month induction period) and during the final 6 months of the same 1-year period (1994–1995). Mean effective doses of risperidone declined during the first year of use, with a mean of 5.9 mg/day over the first year and 4.0 mg/day over the latter 6 months.

Also in 1999, Kozma et al.[13] provided data from the South Carolina Medicaid database on 433 patients with initial prescriptions for risperidone during 1997. Previous evidence had suggested that risperidone was not being dosed according to its package insert guidelines. In their study, risperidone was being prescribed at 47% of its recommended package insert dose, i.e., an average dose of 2.8 mg/day as opposed to 6 mg/day. The reason for this apparent low dosing is unclear but is likely to be because a satisfactory response:tolerability ratio had been achieved at these lower doses. In addition, Schwartz et al.[14] retrospectively reviewed the records of 67 outpatients receiving risperidone at the Veterans Affairs Medical Center in Syracuse, N.Y. The mean dose was 3.8 mg/day.

Nightengale et al.[15] analyzed prescription and medical claims for 640 patients with schizophrenia in a state Medicaid program over a 1-year period and found that the mean daily dose of risperidone remained relatively constant (range, 4.8–5.4 mg). The weighted average daily dose was 5.1 mg.

Table 1 summarizes each of these evaluations. These data clearly indicate that doses of risperidone of 4 to 6 mg/day are more appropriate than the earlier, original higher range recommendations. Recent positron emission tomography (PET) studies have provided a scientific rationale in support of the clinical observations relating to those of lower doses.

PET SCAN DATA

Risperidone differs from the conventional neuroleptics in that it shows a higher affinity for the 5-HT_2 receptor than for the D_2 receptor.[16] It also differs from conventional agents in its low incidence of EPS.[1,2] It has been shown that EPS are related to level of D_2 receptor occupancy.[17] Kapur et al.[18] studied 9 patients receiving 2 to 6 mg/day risperidone using [^{11}C]-raclopride PET scans in order to determine the in vivo D_2 receptor binding characteristics of risperidone. At doses of 4 to 6 mg daily, the in vivo D_2 receptor occupancy of risperidone was similar to that of conventional neuroleptics; this finding, in the authors' view, suggested that the EPS benefits of risperidone cannot be explained solely by low D_2 receptor binding but may be related to its high 5-HT_2 affinity. In patients who received 6 mg of risperidone daily and who had the highest levels of D_2 receptor occupancy, mild EPS were observed, suggesting that the high 5-HT_2 affinity of risperidone provides only a relative protection from EPS. Once D_2 receptor occupancy exceeds 80%, this relative 5-HT_2–mediated protection may be lost. In a further study by Kapur et al.,[19] [^{11}C]-raclopride PET scans were used to compare the D_2 and 5-HT_2 receptor occupancies of clozapine, risperidone, and olanzapine in patients with schizophrenia (N = 44) receiving these drugs in multiple-dose, steady-state regimens. Patients receiving 5 mg of risperidone daily showed equal D_2 occupancy to those receiving 20 mg of olanzapine daily, but greater occupancy than with 75 to 900 mg/day of clozapine. It had previously been suggested that a threshold of D_2 receptor occupancy is required to obtain a satisfactory antipsychotic response[17] and that this threshold lies in the range of 65% to 70%.[20,21] The authors noted that risperidone becomes an effective antipsychotic at doses that cross these levels of receptor occupancy, that is, at doses greater than 2 mg/day.

Table 1. Evolution of Prescribed Dosages of Risperidone Between 1993 and 1999

Study	Study Type	Population	Dosage/day
Chouinard et al, 1993[1]	Double blind	135 chronic schizophrenic patients	6 mg optimal dose
Marder and Meibach, 1994[2]	Double blind	388 schizophrenic patients	6 mg optimal dose
Albus et al, 1997[5]	Phase 4	886 chronic schizophrenic patients	4.8 mg[a], lower in drug-naive patients
Jeste et al, 1997[6]	Phase 4	945 schizophrenic patients	5.9 mg[a]
Love et al, 1999[7]	Clinical audit/ naturalistic	1056 psychiatric patients	5.12 mg[a], more patients with lower doses discharged
Chouinard et al, 1998[8]	Phase 4	330 schizophrenic outpatients	6.1 mg[a], but lower dose effective in many patients
Kasper, 1998[4]	Literature review	Schizophrenic patients	4–6 mg optimal dose range, less in elderly and in first episode
Luchins et al, 1998[9]	Clinical audit/ naturalistic	1283 schizophrenic or schizoaffective patients	5.7 mg[a], discontinuation associated with more rapid titration
Procyshyn and Zerjav, 1998[10]	Clinical audit/ naturalistic	60 psychotic patients	4.9 mg[a]
Chengappa et al, 1999[11]	Clinical audit/ naturalistic	142 psychotic patients, mainly schizophrenic	4.1 mg[a] in discharged patients, 7.5 mg[a] in patients still in hospital
Kelly et al, 1999[12]	Clinical audit/ naturalistic	309 psychiatric patients	5.9 mg[a] in first year, 4.0 mg[a] in second 6 months
Kozma et al, 1999[13]	Clinical audit/ naturalistic	433 patients with risperidone prescriptions	2.8 mg[a]
Schwartz et al, 1999[14]	Clinical audit/ naturalistic	67 outpatients	3.8 mg[a]
Nightengale et al, 1999[15]	Clinical audit/ naturalistic	640 schizophrenic patients	5.1 mg[a]
Lemmens et al, 1999[3]	Meta-analysis of 27 studies	2074 psychotic patients, mainly schizophrenic	No increase in efficacy over 4 mg

[a]Mean values.

Nyberg et al.[22] used [^{11}C]-raclopride PET scans to measure D_2 receptor occupancy and [^{11}C] *N*-methylspiperone scans to measure 5-HT_{2A} receptor occupancy in 8 first-episode or drug-free schizophrenic patients treated with risperidone. At a dose of 6 mg/day, mean D_2 receptor occupancy was 82%, and 6 patients (75%) had developed EPS. After dose reduction to 3 mg/day, 3 patients still exhibited EPS. The authors concluded that treatment with 6 mg/day of risperidone is likely to induce unnecessarily high D_2 receptor occupancy, with a consequent risk of EPS. High 5-HT_{2A} receptor occupancy in their study population did not completely prevent EPS. The authors suggested a threshold for EPS at D_2 occupancy above 80% and that the optimal range of D_2 receptor occupancy is 70% to 80% (Figure 2). Given that EPS only occur at D_2 occupancy greater than that needed for an antipsychotic effect, the 3 patients (37.5%) who developed EPS on 3 mg/day were probably taking too high a dose, while the 3 patients who experienced the disappearance of EPS were probably then taking an appropriate dose.

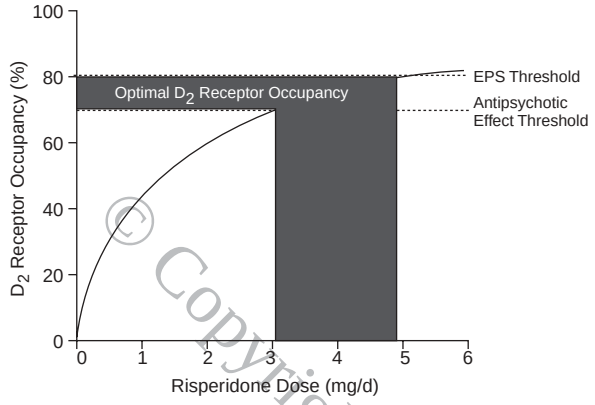
SPECIAL PATIENT GROUPS

First-Episode Patients

Kopala et al.[23] studied 22 first-episode drug-naive patients with schizophrenia (mean age = 25.0 years; range, 17–40 years), and found that 3 patients (14%) had distinct EPS at baseline, whereas all were free of EPS following treatment with risperidone. Patients receiving 2 to 4 mg of risperidone daily showed a superior clinical response compared with that of those receiving 5 to 8 mg daily (Figure 3); 91% of the low-dose group showed a 20% or greater reduction in positive and negative symptom scores as compared with 27% of the high-dose group. With the maximum dose of risperidone (5–8 mg/day), 32% of patients developed mild akathisia or parkinsonian rigidity, both of which were diminished with dosage reduction. In the study group, therefore, risperidone in doses of 2 to 4 mg/day effectively treated positive, negative, and general symptoms of schizophrenia and eliminated preexisting EPS.

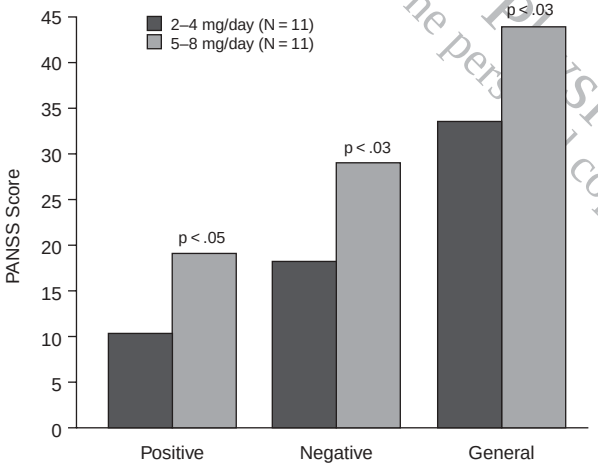
In a dose-finding study[24] of 96 patients with first-episode psychosis who were treated with risperidone, 60% of patients achieved a good response at 4 weeks after commencing treatment with 2 mg/day of risperidone. Increases in dosage to 3 mg/day or 4 mg/day were associated with some additional response, but in the group as a whole, the mean daily dose for the initial 10-week period of treatment was 2.8 mg of risperidone. The investigators found that, in this population, a substantial number of patients started to develop EPS once the dose was elevated above 2 mg/day of risperidone. For first-episode patients

Figure 2. Dopamine D_2 Receptor Occupancy as a Function of Dose Showing Hypothetical Thresholds for Antipsychotic Effect and Extrapyramidal Symptoms (EPS)[a]



[a]Adapted from Nyberg et al.,[22] with permission.

Figure 3. Symptom Scores in First-Episode Patients With Schizophrenia After Treatment With Risperidone[a]



[a]Adapted from Kopala et al.,[23] with permission. Abbreviation: PANSS = Positive and Negative Syndrome Scale.

in particular, emergence of EPS should suggest a dosage reduction to achieve D_2 receptor blockade less than 80%. Specifically, mean D_2 occupancy for 2 mg of risperidone is 66%.[18]

Elderly Patients

Madhusoodanan et al.[25] conducted an open 12-week study to evaluate the tolerability and efficacy of risperidone in 11 elderly patients (mean age = 69 years; range, 61–79 years) with a diagnosis of schizophrenia (75%) or schizoaffective disorder (25%). Patients received an initial dose of 0.5 mg twice daily, increasing in increments of 0.5 mg twice daily to a maximum dose of 3 mg/day during the first week. The dose was adjusted on day 8. Mean risperidone dose at endpoint was 2.4 mg/day. Positive and negative symptom scores improved significantly both in patients receiving ≤ 3 mg/day and ≥ 3 mg/day risperidone. The most common adverse effect was dizziness (in 22% of patients); no clinically significant abnormalities in vital signs or laboratory test results were reported.

Zarate et al.[26] reviewed the medical records of 122 hospitalized psychogeriatric patients (mean age = 76 years; range, 65–95 years) newly treated with risperidone. The patients were given risperidone for agitation or psychosis associated with dementia (53%), major mood disorder (29%), or other disorders (18%). In common with other elderly mentally ill populations,[27] most of the patients (77%) were also medically ill and were receiving cardiovascular (70%) or other psychotropic agents (76%). Daily doses of risperidone averaged 1.6 mg (range, 0.25–8.0 mg); 78% of patients received 2.0 mg daily. Risperidone appeared effective in 85% of cases, but 11% were discontinued because of intolerance and 7% because of inefficacy. The most common adverse event was hypotension (29% of those discontinued). Adverse events were associated with cardiovascular disease and its treatment, cotreatment with a selective serotonin reuptake inhibitor or valproate, and relatively rapid dose increases. In all, 13 patients developed EPS, an indication that the dosage used was higher than clinically necessary. The average dosage was reduced from 2.1 to 1.7 mg in this population, and no new EPS were seen in patients given 2 mg or less of risperidone.

The authors suggested that previous dosage regimens, which specified daily increases of 1 mg twice daily titrating to 6 mg/day within 3 days, were probably excessive for elderly patients and that dosing at even half that rate may be excessive for many elderly patients.[26] Their results indicated that slowly increased doses of risperidone were better tolerated, and the authors suggested an initial dose of risperidone as low as 0.125 mg once or twice daily, increased in increments of 0.125 mg once or twice daily at intervals of not less than 3 days. In their study, many patients responded to daily doses of risperidone of only 1 to 2 mg. They recommended a target dose of 1 mg/day.[26]

Zarate et al.[26] set out the following guidelines for elderly groups:

- Elderly patients require thoughtful medical evaluation before treatment with risperidone, especially if taking other medications.
- All medication, especially cardiovascular drugs and central nervous system depressants, should be reviewed for elimination or reduction to minimum effective doses before risperidone is added.
- Warning signs of impending risperidone intolerance include dizziness, confusion, or bradykinesia. Sitting and standing blood pressure should be monitored until risperidone dosage is stabilized.

- Dosing may need to be even more conservative in elderly (and other) patients receiving adrenergic antagonists, calcium channel blockers, acetylcholin esterase inhibitors, other vasodilators, diuretics, antidepressants, or valproate.

Chanlam et al.[28] investigated long-term efficacy, safety, and tolerability of risperidone in 180 elderly psychotic patients (median age = 72 years) in a 12-month multinational open-label trial. The majority of patients (94%) had a diagnosis of schizophrenia, and the remainder (6%) were diagnosed with schizophreniform disorder. Most patients (92%) were hospitalized at the start of the trial. The initial dose of risperidone, 0.5 mg twice daily (oral solution), was increased to 1.5 mg twice daily during week 1, after which doses were adjusted according to each patient's response to treatment to a maximum of 4 mg twice daily. The mean dose of risperidone at endpoint was 3.7 mg/day. Clinical improvement as assessed by the Positive and Negative Syndrome Scale was achieved by 41% of patients after 4 weeks of treatment and by 54% at 12 months. Severity of EPS decreased significantly from baseline to endpoint ($p < .001$), and use of antiparkinsonian medication decreased from 41% of patients before the trial to 25% during the trial. Reported adverse events (leading to 30 patients' dropping out) not unequivocally related to study medication included insomnia, agitation, and urinary tract infections, but there were no reports of tardive dyskinesia during the 1-year trial. Patients receiving a modal dose between 3 mg and 4 mg risperidone daily obtained the best clinical improvements.

However, Pollock et al.[29] counseled against the assumption that the elderly will invariably benefit from a reduced dose; there is greater metabolic variance in the elderly,[30] and some may be extensive metabolizers of risperidone.[31] Conservative dosage regimens similar to those in the elderly are recommended in patients with impaired renal or hepatic function.[32]

Dementia

Results of 2 large clinical trials[33,34] have recently been reported demonstrating efficacy, tolerability, and safety of risperidone in elderly patients with dementia. The first study[33] was a U.S.-based, fixed-dose, double-blind, 12-week trial that involved more than 600 nursing home patients and compared the effect of placebo with that of 0.5 to 2 mg/day risperidone titrated to the target dose. The second trial,[34] based in Europe and Canada, was a flexible-dose study in which risperidone was initiated at 0.5 mg/day, with increments of 0.25 mg every 4 days to a maximum of 4 mg/day, according to the judgment of the physician. The symptoms displayed by patients in the 2 studies were similar; aggression and wandering were among the most severe, but delusions, hallucinations, anxiety, affective symptoms, and diurnal rhythm disturbances were also apparent. Risperidone had 2 separate effects in dementia: an antipsychotic effect and an antiagitation or antiaggression effect. The improvement in aggressive symptoms with risperidone was apparent even at the lowest dose of 0.5 mg/day.[33] Psychotic symptoms also improved, and the effects of 1- and 2-mg/day doses of risperidone were superior to those of placebo.[33] Severity of EPS with risperidone was dose related and, at 1 mg/day,[33] and a mean of 1.1 mg/day[34] was comparable to that with placebo.

Bipolar Disorder

Ideal doses of risperidone in bipolar disorder have not yet been fully established in clinical practice, or indeed in published phase 3 clinical trials. Original open-label and case series studies showing positive efficacy of risperidone in mania used the following mean risperidone doses per day: 2.75 mg,[35] 3.2 mg,[36] 3.5 mg,[37] and 4.9 mg.[25] A double-blind trial[38] of risperidone in the treatment of bipolar disorder used a fixed dose of 6 mg/day. These trials were all short-term studies conducted in small numbers of patients. The largest published trial,[39] which included 541 patients with bipolar disorder or schizoaffective disorder treated with open-label risperidone for 6 months, used a mean modal dose of risperidone of 3.9 mg/day. Further data are needed to establish an appropriate dose of risperidone in bipolar disorder and in specific patient types, such as those with acute mania and those who have bipolar disorder with psychotic symptoms. Studies of maintenance therapy with risperidone in bipolar disorder are awaited particularly because the question of which patients benefit from long-term treatment is of much current interest.

SUMMARY AND DOSAGE GUIDANCE

Risperidone is an effective and relatively well-tolerated novel antipsychotic drug. Evidence from naturalistic trials and from 5 years of practical experience has prompted a reassessment of risperidone dosing practice. On the basis of this new evidence, current dosing recommendations can be summarized as follows.

Schizophrenia in Otherwise Healthy Adults

In patients not previously exposed to risperidone, a starting dose of 1 to 2 mg/day is recommended, with dose increases in increments of 0.5 to 1 mg/day titrated over 6 to 7 days to a target dose for most patients of 4 mg/day, although individual exceptions may be sometimes needed to achieve an optimal balance between efficacy and tolerability. Doses higher than 6 mg/day are unlikely to bring further improvement in most patients and are associated with more EPS.[40] Indeed, EPS requiring anticholinergic treatment obscure the inherent low muscarinic activity of risperidone.

Table 2. Summary of Risperidone and Recommendations[a]

Patient Population	Starting Dose (mg/d)	Target Dose (mg/d)	Maximum Dose (mg/d)
Schizophrenia	1–2	4	6
First-episode	1	2	4
Elderly	0.25	2	4
BPSD	0.5	1	1.5

[a]Abbreviation: BPSD = behavioral and psychological symptoms of dementia.

No data at present support a dose reduction in patients whose symptoms have become well controlled and stabilized at a low level. The current evidence suggests that the majority of patients continue to derive benefit from a risperidone dose of 4 mg/day,[41] although dose ranges between 1 and 8 mg have been used in some patients during the maintenance phase according to their longer-term clinical need.

No specific data at present enable the evaluation of the effect of dose escalation during an acute exacerbation. Daily doses of 5 to 6 mg have been reported to be effective in reducing symptoms associated with acute exacerbation,[42] although in the population evaluated in that particular study, preexacerbation dose data are not known.

First-Episode Patients

On the basis of current evidence, first-episode and younger patients appear to benefit optimally from risperidone at doses of 1 to 3 mg/day. The current evidence supports a starting dose of 1 mg/day with an initial target dose of 2 mg/day. Slow titration to 4 mg/day may be necessary, according to clinical response at lower doses and neurologic side effects at higher doses.

Elderly Patients

The current dose recommendation in the elderly is to commence with 0.25 mg/day, using a slow titration; generally a dose of 2 mg/day will provide adequate response, although some patients may need 3 or 4 mg.

Other Patient Populations

On the basis of effectiveness and absence of significant EPS, a dose of 1 mg/day of risperidone has been recommended as the target dose for patients with behavioral and psychological symptoms of dementia.[33] Considering clinical experience of patients with dementia, the following guidelines are suggested:

- Start with 0.5 mg/day risperidone (in the evening)
- Stay at this dose for at least 2 days
- Increase to target dose (1 mg/day)
- Titrate between 0.5 mg and 1.5 mg/day

Recommended doses of risperidone in bipolar disorder have not yet been fully established, but judging by the results of clinical trials so far, these doses are likely to be 1 to 4 mg/day or lower.

Other Issues About Dosing

Dosing schedule. Risperidone is usually given as a once-daily oral dosage for convenience. However, in vulnerable populations, such as the elderly, there is no prima facie reason why the total daily dose of risperidone cannot be given in a twice-daily schedule. This may be helpful when unwanted effects may be related to peak plasma levels. No objective data are available for a more frequent daily dosage schedule than this.

Dose modification for side effects. In the event of a nonserious unwanted adverse event that may be dose related or due to a too-rapid titration and in patients who otherwise have the potential to respond to risperidone, a dose reduction may be feasible. The aim of this tactic is to strike an optimal balance between efficacy and tolerability without prematurely discontinuing the drug.

CONCLUSION

Based on these recent data, the revised recommended target dose of risperidone of 4 mg/day for most patients with schizophrenia and less-rapid dose titration than previously recommended are well justified.[43] A lower dose and slower titration may be appropriate for the elderly, first-episode younger patients, and some other patient populations (Table 2). With this updated recommendation, optimal dosing is more likely to be achieved so that the benefit:risk ratio of risperidone is likely to be enhanced.

Drug names: clozapine (Clozaril and others), olanzapine (Zyprexa), risperidone (Risperdal).

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