

Risperidone Side Effects

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The overall effectiveness of traditional antipsychotics has been hindered by their extrapyramidal side effects, which contribute to noncompliance and relapse in patients with schizophrenia. The side effects associated with traditional antipsychotic treatment are generally minimal in patients who take risperidone, a combined 5-HT₂/D₂ antagonist, but the literature is sparse on adverse events among the newer atypical antipsychotics. Risperidone is associated with relatively few motor side effects compared with the traditional antipsychotics, and weight gain is less likely with risperidone than with either clozapine or olanzapine. While increased prolactin levels have been reported in patients taking risperidone, little correlation has been found between prolactin levels and adverse events. As antipsychotic treatment options expand to include the new agents, it is important for clinicians to anticipate side effects and to query patients about specific adverse events.

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Antipsychotics are life-altering drugs. Because of adverse side effects and the need for frequent blood sampling (when clozapine is administered), patients' lives are substantially driven by the medications used to treat their psychiatric illnesses. A core focus of novel psychiatric drug development has been the synthesis of compounds that have maximum therapeutic effects and minimal or no side effects. As a result of this effort, the side effects of new atypical antipsychotics differ in scope and severity from those associated with older traditional agents. In general, the complications associated with traditional antipsychotic treatment are minimal in patients who take risperidone, which is a combined 5-HT₂/D₂ antagonist and was the first atypical antipsychotic to be approved by the Food and Drug Administration for unrestricted use in schizophrenia. Unlike clozapine, risperidone lacks anticholinergic effects and does not appear to cause agranulocytosis. It is associated with relatively few motor side effects compared with traditional antipsychotics and is effective against both the positive and negative symptoms of schizophrenia. This profile has led to considerable optimism over the therapeutic role of risperidone in patients who have treatment-resistant refractory psychosis. Because atypical antipsychotics have only been available for a short time, the literature is sparse

on incidence rates of their adverse effects. Moreover, conclusions from different clinical trials may vary depending on whether data are gathered by spontaneous reporting or by clinician-initiated inquiry. Therefore, as antipsychotic treatment options expand to include the new agents, it is important for clinicians to anticipate side effects and to query patients about specific adverse events.

EFFICACY OF RISPERIDONE

Pivotal randomized double-blind comparisons of the atypical antipsychotic risperidone versus the traditional antipsychotic haloperidol—primarily a D₂ antagonist—were reported in the early 1990s. One of the studies¹ was in schizophrenic patients with acute exacerbation of illness; the other studies involved patients with stable, chronic schizophrenia.^{2–4} The North American Study was conducted in several centers in Canada and the United States, and the 2 limbs of the study were reported separately.^{2,3} The Multinational Study was conducted in 15 countries in Europe, Central and South America, and South Africa.⁴ In these studies, risperidone, which acts primarily by the blockade of the 5-HT_{2A} receptor, was found to improve positive and negative symptoms of schizophrenia compared with placebo and active controls. A later meta-analysis of the randomized controlled trials⁵ reported that the atypical antipsychotics risperidone and olanzapine, but not quetiapine, are slightly more effective than haloperidol in the treatment of global psychopathology and negative symptoms of schizophrenia.

Studies have also reported risperidone to be more effective than conventional antipsychotics in the treatment of refractory illness and of negative symptoms. After 4 weeks of treatment, overall improvement as assessed by the Brief Psychiatric Rating Scale was significantly better

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in medication-unresponsive patients treated with 6 mg/day of risperidone ($N = 34$) than with 15 mg/day of haloperidol ($N = 33$).⁶ Additional evidence suggests that the efficacy of risperidone is superior to that of conventional agents in refractory patients.⁷ A meta-analysis of pooled results from 6 double-blind clinical trials⁸ showed that risperidone at doses ranging from 4 to 8 mg/day had a significantly higher negative symptom response rate, as defined as the percentage of patients with a 20% or greater reduction in scores on the negative subscale of the Positive and Negative Syndrome Scale (PANSS), than patients receiving active controls including haloperidol, perphenazine, or zuclopenthixol.

The efficacy and safety of risperidone versus olanzapine were compared recently in a large, multisite, double-blind study.⁹ After a 1-week washout period, 407 patients with DSM-IV schizophrenia or schizoaffective disorder were randomly assigned to receive flexible doses of risperidone (2–6 mg/day) or olanzapine (5–20 mg/day) for 8 weeks. Assessment measures included the PANSS, the Extrapyramidal Symptom Rating Scale (ESRS), and standard laboratory tests. At week 8, risperidone-treated patients showed significantly greater improvements than olanzapine-treated patients on the positive symptom subscale and the affective symptom subscale. Both groups showed significant symptom improvement in total PANSS scores and in the 5 PANSS subscales.

In a head-to-head effectiveness study comparing risperidone and olanzapine,¹⁰ the 2 atypical antipsychotics were equally effective as acute treatment for DSM-IV schizophrenia, but risperidone was more effective for treatment of psychotic symptoms at 6 months. Symptoms of schizophrenia, global functioning, and extrapyramidal symptoms (EPS) were assessed before and after acute open-label treatment with risperidone ($N = 21$) and olanzapine ($N = 21$). After an average of 4 weeks, both risperidone and olanzapine were effective in reducing negative, psychotic, and disorganized symptoms and there were low rates of treatment-emergent parkinsonism with both drugs. While the 2 agents were similarly effective in the treatment of negative and disorganized symptoms at 6 months, risperidone was significantly more effective than olanzapine in the reduction of psychotic symptoms in the 13 risperidone-treated and 13 olanzapine-treated subjects available for follow-up. The mean \pm SD dose at follow-up was 4.5 ± 2.3 mg/day of risperidone and 13.8 ± 7.6 mg/day of olanzapine.

ADVERSE EFFECTS

EPS and Tardive Dyskinesia

The overall effectiveness of traditional antipsychotics has been hindered by their EPS, which contribute to non-compliance and relapse in schizophrenic patients. The atypical antipsychotics generally have low rates of EPS. In

the clinical trials of risperidone, the overall ESRS and subscale scores at baseline were similar, and patients taking risperidone consistently exhibited a lower rate of EPS on the questionnaire than those patients taking haloperidol.^{2,4}

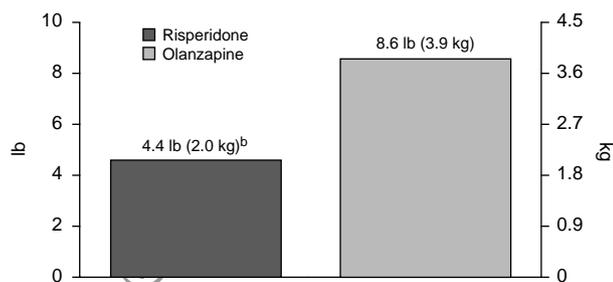
There is an apparent dose-related increase in EPS in patients who take risperidone.³ Risperidone doses up to 16 mg/day were evaluated in clinical trials; however, the current prescribing information recommends between 4 and 8 mg/day of risperidone for maximal effect.¹¹ Although large well-designed comparative studies using clinically relevant doses of the atypical agents are sparse, one recent head-to-head study of risperidone versus olanzapine in 42 patients with schizophrenia¹⁰ found the 2 medications to have comparable rates of parkinsonian side effects after 6 months of follow-up. There was no statistically significant difference in the rate of adverse events due to EPS in a large, multisite, double-blind comparison of risperidone and olanzapine.⁹ An analysis of factors associated with EPS in 12 double-blind studies of risperidone versus placebo and conventional antipsychotics¹² reported that the mean change from baseline to worst score on the ESRS was similar for patients receiving 4 to 8 mg/day of risperidone and for those receiving placebo.

Traditional neuroleptics appear to carry similar liability for tardive dyskinesia. In young, healthy adults, the annual cumulative incidence of tardive dyskinesia is 4% to 5%,¹³ which increases to around 30% in older adults.¹⁴ Atypical antipsychotics appear to carry a low liability for tardive dyskinesia. An open-label study of the first 3 years of risperidone use in 1100 patients, 503 of whom had taken risperidone for at least 1 year, reported an annual incidence of tardive dyskinesia of 0.3% in patients taking 7.6 to 9.4 mg/day of risperidone.¹⁵ A combined analysis of risperidone studies¹² reported 2 cases of tardive dyskinesia among 882 patients who received at least 12 weeks of risperidone treatment.

Weight Gain

Weight gain is likely to be problematic in patients taking atypical antipsychotics just as it is with traditional antipsychotic treatment.¹⁶ When chlorpromazine was first introduced, the large majority of patients treated with the drug gained considerable weight, and similar problems have occurred in varying degrees with all antipsychotic agents. In a meta-analysis of weight gain associated with antipsychotic treatment, Allison et al.¹⁷ reported that after 10 weeks of treatment, thioridazine was associated with the greatest weight increase (3.25 kg). The mean increases among the newer antipsychotics were 4.46 kg for clozapine, 4.15 kg for olanzapine, and 2.10 kg for risperidone. In a head-to-head study of risperidone versus olanzapine,⁹ increases in body weight and body mass index (BMI) were significantly greater in the olanzapine group (mean weight increase = 3.9 kg, mean BMI increase = 1.3 kg/m^2) than in the risperidone group (mean weight increase = 2.0 kg,

Figure 1. Risperidone vs. Olanzapine: Mean Change From Baseline in Weight at Week 8^a



^aFrom Conley and Mahmoud,⁹ with permission.

^bOlanzapine patients had significantly greater increases in mean body weight ($p < .001$). 95% Confidence interval (difference of excess weight in olanzapine group) = (2.3, 7.1).

mean BMI increase = 0.7 kg/m²; Figure 1). Weight gain is often a factor in noncompliance and has long-term consequences of medical morbidity. Observations suggest that the longer the duration of clozapine treatment, the greater the weight gain.¹⁸

Weight gain may be more of an issue with some patients than others, and physicians should consider weight gain liability, and particularly the potential for diabetes, before selecting an antipsychotic. Several reports have associated new onset diabetes with olanzapine^{19,20} and clozapine^{19,21} treatment. Patients and their families should be informed of the possibility for weight gain when taking antipsychotic medications. Likewise, it is important for the clinical team to develop behavioral and educational strategies to help patients manage the weight issues.

Hyperprolactinemia

Hyperprolactinemia is a common clinical disorder that may arise from a variety of etiologies; it occurs in patients taking antipsychotics, presumably because of dopamine receptor blockade. Kleinberg et al.²² analyzed data of adverse events possibly associated with increased prolactin levels—i.e., amenorrhea, galactorrhea, and decreased libido in women and erectile dysfunction, ejaculatory dysfunction, gynecomastia, and decreased libido in men—from the North American and Multinational Studies of risperidone treatment in schizophrenic patients in which both risperidone and haloperidol produced dose-related increases in serum prolactin levels in men and women. The risperidone dose was not correlated with adverse events among women, nor were the adverse events correlated with endpoint prolactin levels. Among men, the incidence of adverse events was positively correlated with risperidone dose; however, at risperidone doses of 4 to 10 mg/day, the incidence of adverse events was not significantly higher than that observed in patients receiving placebo. Moreover, adverse events in men were unrelated to plasma prolactin levels. The authors concluded that a risperidone-

associated increase in serum prolactin level was not significantly correlated to the emergence of possible prolactin-related side effects.

In the large, multisite, head-to-head comparison of risperidone and olanzapine,⁹ more patients had elevated serum prolactin levels in the risperidone group than in the olanzapine group, but few patients in either group reported prolactin-related adverse events.

Hyperprolactinemia becomes problematic when it causes sexual dysfunction in patients taking antipsychotics.²² Amenorrhea, ejaculatory dysfunction, and/or erectile dysfunction may inhibit sexual fulfillment, lead to infertility, and foster noncompliance. Additionally, hyperprolactinemia may mask a prolactinoma or other non-neuroleptic cause of elevated serum prolactin levels; therefore, the treating physician should consider the possibility of a pituitary tumor in assessing patients with this finding. When hyperprolactinemia occurs in young women with amenorrhea, the condition may be associated with osteopenia.²³ Bone loss also occurs in men with prolactinomas and high circulating prolactin levels. Whether bone loss and bone resorption in older women with low estrogen levels are prolactin related remains undetermined. Given the fact that schizophrenic patients are generally at high risk for falls and accidents, there appears to be no association between the chronic administration of antipsychotics and an increased incidence of pathologic fractures. In patients with hyperprolactinemia and sexual dysfunction, dose reduction or switching to another antipsychotic agent should be considered.

Other Side Effects

Other side effects that have been reported include sedation at the beginning of risperidone treatment and agitation. Sedation is seldom a problem for most patients who take atypical antipsychotics long-term. Risperidone is usually sedating only when titration is rapid; only 3% of patients reported somnolence at the optimal dosage of 6 mg/day in the Marder and Meibach study.² In the North American trial of olanzapine, somnolence occurred in 39% of 69 patients taking 15 ± 2.5 mg/day,²⁴ and in a head-to-head study of clozapine versus risperidone, 20 outpatients complained of more insomnia with risperidone and more sedation with clozapine.²⁵ It has been suggested that risperidone possesses acute antimanic efficacy²⁶; other data indicate that the drug may induce or exacerbate manic symptoms, especially when given in high doses and without concomitant mood stabilizers.^{26,27}

When insomnia, sedation, or agitation occurs, the clinician must determine if these symptoms are an intrinsic feature of the new drug or the possible result of switching drugs and treat accordingly. In the overall management of the side effects of risperidone, the manner in which treatment-refractory patients are transitioned between their preceding antipsychotic and risperidone may play

a major role in the success of the endeavor. When appropriate, a slow cross-tapering of antipsychotics in addition to adjunctive antiparkinsonian agents, benzodiazepines, or anticholinergic medication may enhance the success of the transition.

A change in electrical conduction of the myocardium—i.e., prolongation of the QTc interval—is another effect of some antipsychotic medications and probably occurs because of alterations in ion channels in the myocardium. Patients may be vulnerable to cardiac conduction irregularities particularly during repolarization when the heart is sensitive to tachyarrhythmias. However, data from 3 short-term, double-blind studies and 7 long-term studies indicate that mean QTc changes in patients receiving risperidone were negative or minimally positive.²⁸ Additionally, changes in QTc interval were similar in patients receiving risperidone, placebo, and haloperidol.

CONCLUSION

In general, the side effects associated with traditional antipsychotics are minimal in patients who take risperidone, but the literature is sparse on adverse effects among the new atypical antipsychotics. Risperidone was reported to be more effective than olanzapine in treating positive symptoms of schizophrenia and to have a similar rate of extrapyramidal side effects as olanzapine in 2 head-to-head studies.^{9,10} The annual incidence of tardive dyskinesia was reported to be 0.3% in patients taking 7.6 to 9.4 mg/day of risperidone for at least 1 year.¹⁵ The successful management of risperidone side effects may be influenced by the manner in which patients are transitioned between their preceding antipsychotic and risperidone therapy.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

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

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