Risperidone in the treatment of bipolar mania

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Abstract: Atypical antipsychotic medications have assumed growing importance for the treatment of bipolar disorder, an illness that affects approximately 1.2%–3.7% of the general population in a given year. Current practice guidelines for the treatment of bipolar mania support the use of atypical antipsychotic medications as monotherapy or as a component of polytherapy, and in clinical settings the use of atypical antipsychotics to treat bipolar disorder is widespread. Risperidone is an atypical antipsychotic, sometimes referred to as a second-generation antipsychotic. The receptor-binding profile of risperidone, which includes potent antagonism of the serotonin 5-$HT2_A$, dopamine D_2, and alpha-adrenergic receptors, is believed to be related to positive effects on mood. The FDA-approved bipolar indications for risperidone include: 1) monotherapy for short-term treatment of acute manic or mixed episodes associated with bipolar I disorder and 2) combination therapy with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder. This review of risperidone for bipolar mania will address the chemistry, pharmacodynamics, pharmacokinetics, and metabolism of risperidone, use with concomitant medications, clinical trials in bipolar mania, as well as safety and tolerability issues. Finally, dosing and administration are addressed as well as use for bipolar mania in geriatric, child, or adolescent patients.

Keywords: risperidone, bipolar disorder, mania, antipsychotic, psychopharmacology

Introduction

Atypical antipsychotic medications have assumed growing importance for the treatment of bipolar disorder, an illness that affects approximately 1.2%–3.7% of the general population in a given year (Regier et al 1993; Hirschfeld et al 2003). For bipolar mania in particular, the atypical antipsychotics have demonstrated efficacy and generally good tolerability. Current practice guidelines for the treatment of bipolar mania support the use of atypical antipsychotic medications as monotherapy or as a component of polytherapy (APA 2002). In clinical settings the use of atypical antipsychotics to treat bipolar disorder is widespread. A recent report based upon a large US registry of over 65 000 individuals with bipolar disorder noted that in 2001, more than 40% of individuals with bipolar disorder were prescribed antipsychotic medications, and that 85% of these were on atypical antipsychotics (Sajatovic et al 2004).

Most published bipolar disorder treatment trials focus on the use of atypical antipsychotics as anti-manic agents, although literature on the use of atypical antipsychotics in other phases of bipolar disorder illness is accumulating (Calabrese et al 2005). In 2000, olanzapine was the first atypical antipsychotic to receive a Food and Drug Administration (FDA) bipolar mania indication. Subsequent FDA approvals for bipolar mania indications were received for risperidone in 2003 and 3 additional compounds in 2004, quetiapine, ziprasidone, and aripiprazole.

Risperidone is an atypical antipsychotic, sometimes referred to as a second-generation antipsychotic. While it was the second atypical antipsychotic to come to

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the US market overall, risperidone was the first atypical antipsychotic recommended as a first-line treatment for the management of schizophrenia. The receptor-binding profile of risperidone, which includes potent antagonism of the serotonin 5-HT2_A, dopamine D_2, and alpha-adrenergic receptors, is believed to be related to positive effects on mood (Leyson et al 1994; Pania and Gessab 2002; Kalkman and Loetscher 2003; Hirschfeld et al 2004). The FDA-approved bipolar indications for risperidone include: 1) monotherapy for short-term treatment of acute manic or mixed episodes associated with bipolar I disorder and 2) combination therapy with lithium or valproate for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder.

This review of risperidone for bipolar mania will address the chemistry, pharmacodynamics, pharmacokinetics, and metabolism of risperidone, use with concomitant medications, clinical trials in bipolar mania, as well as safety and tolerability issues. Finally, dosing and administration are addressed as well as use for bipolar mania in geriatric, child, or adolescent patients, which are unapproved off-label uses at this time.

Chemistry of risperidone

Risperidone is a benzisoxazole antipsychotic. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49.

Pharmacodynamics, pharmacokinetics, and metabolism of risperidone

Risperidone is a selective monoaminergic antagonist with high affinity (Ki 0.12–7.3 nM) for the 5-HT_2, D_2, alpha$_1$, and alpha$_2$ adrenergic and H_1 histaminergic receptors. It has low to moderate affinity (Ki 253 nM) for the serotonin (5-HT_{1c}, 5-HT_{1d}, and 5-HT_{1a}) receptors, weak affinity (Ki 620–800 nM) for the dopamine D_1 and the haloperidol-sensitive sigma site, and no affinity for cholinergic muscarinic or B_1 and B_2 adrenergic receptors.

Risperidone is well absorbed. Food does not affect the rate and extent of absorption. The absolute oral bioavailability of risperidone solution is 70%. Bioavailability of the oral tablets as well as the orally disintegrating tablets is 66%. Plasma concentrations of risperidone, 9-hydroxyrisperidone (its major active metabolite), and the combination of risperidone and 9-hydroxyrisperidone are dose proportional over the dosage range of 1–16 mg/day. Peak plasma concentrations occur at about 1 hour in extensive metabolizers and 3 hours in poor metabolizers.

Risperidone is bound to albumin and alpha$_1$-acid glycoprotein. The plasma-protein binding of risperidone is 90% while the 9-hydroxyrisperidone metabolite is 77% bound. Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone via the enzyme CYP2D6. The rate of metabolism through CYP2D6 is dependent on genetic polymorphism (Janssen Pharmaceuticals 2003b). The main metabolite, 9-hydroxy-risperidone, has similar pharmacological activity to risperidone. Therefore, the clinical effects of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone (active moiety). Risperidone and its metabolites are eliminated via the urine and to a much lesser extent via the feces. The half-lives of risperidone and 9-hydroxyrisperidone are 3 hours and 21 hours, respectively, in extensive metabolizers, and 20 hours and 30 hours, respectively, in patients who are poor metabolizers. The overall mean elimination half-life of the active moiety is approximately 20 hours.

Risperidone is available as a standard oral tablet, a fast-dissolving tablet, and an oral solution, as well as a long-acting injection. Alternatives to a standard oral formulation may be of particular use in situations where patients may have difficulty swallowing pills or where medication adherence is a concern. The long-acting dosage formulation uses the extended-release Medisorb (Medisorb Technologies International LP, Cincinnati OH, USA) drug-delivery system: small polymeric microspheres degrade slowly, releasing the medication at a controlled rate. The long-acting injection of risperidone exhibits different pharmacokinetics from the standard oral formulation. After a single intramuscular injection there is a small initial release of drug (< 1% of the dose), followed by a lag time of 3 weeks and subsequent release of risperidone. Therefore, oral antipsychotic supplementation should be given for at least 3 weeks after the administration of the initial intramuscular injection of long-acting risperidone to maintain therapeutic levels until the main release of risperidone from the injection site has begun (Janssen Pharmaceuticals 2003a).

The apparent half-life of risperidone plus 9-hydroxy-risperidone following intramuscular administration is 3–6 days and is associated with a monoexponential decline in plasma concentrations. This half-life is the result of

microsphere erosion and subsequent absorption of risperidone. The elimination phase is complete 7–8 weeks after the last injection. Steady-state plasma concentrations of the long-acting intramuscular dosage form are reached after 4 injections and are maintained for 4–6 weeks after the last injection. Similar to the oral dosage form of risperidone, plasma concentrations of the intramuscular form of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are linear over the dosing range of 25–50 mg. The combination of the release profile and the dosage regimen (intramuscular injections every 2 weeks) of long-acting risperidone results in sustained therapeutic concentrations.

Patients with either renal or hepatic disease have not been studied using long-acting risperidone. Based on the studies with oral risperidone, it is recommended that these patients be carefully titrated on oral risperidone before starting on long-acting risperidone. Elderly patients, who can tolerate 2 mg/day, can be started on 25 mg every 2 weeks and maintained on the regular dosing schedule.

Use of risperidone with concomitant medications

Risperidone, a CYP2D6 substrate, could be subject to 2 kinds of drug–drug interactions (Janssen Pharmaceuticals 2003b). First, inhibitors of CYP2D6 interfere with the conversion of risperidone to 9-hydroxyrisperidone. Examples of drugs that inhibit CYP2D6, and therefore risperidone metabolism, include fluoxetine and paroxetine. Combined use of risperidone and one of these SSRIs will require the clinician to review risperidone dosing and the patient's clinical status. A dosage adjustment may be needed. The second type of drug–drug interaction could result from co-administration of risperidone with a known enzyme inducer such as carbamazepine, phenytoin, rifampin, or phenobarbital. This co-administration could result in a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. For example, plasma concentrations of risperidone and 9-hydroxyrisperidone may be decreased by 50% with concomitant use of carbamazepine. If carbamazepine is initiated a dosage increase may be needed. Conversely, if carbamazepine is discontinued, a decrease in dosage may be needed. Of relevance to the treatment of patients with bipolar disorder, risperidone does not appear to interact with lithium or valproate. Table 1 summarizes selected potential important drug interactions with risperidone.

Table 1 Psychiatric drug interactions with risperidone: selected agents affecting risperidone levels

Decrease risperidone levels	Increase risperidone levels
carbamazepine	chlorpromazine
	clomipramine
	clozapine
	desipramine
	duloxetine
	fluoxetine
	haloperidol
	imipramine
	paroxetine
	pergolide
	ropinirole
	sertraline
	trazodone
	verapamil

Clinical trials in bipolar mania

A number of double-blind, randomized, controlled trials (RCTs) and open-label trials of risperidone as monotherapy and in combination with mood stabilizers have been conducted with patients with bipolar disorders (Segal et al 1998; Guille et al 2000; Licht et al 2001; Stahl and Shelton 2001; Vieta et al 2001, 2002, 2004; Sachs 2002; Hirschfeld et al 2003; Yatham et al 2003; Bowden et al 2004; Hirschfield et al 2004; Ghaemi et al 2004; McIntyre et al 2004; Petrie 2004; Shelton and Stahl 2004; Gopal et al 2005; Khanna et al 2005; Smulevich et al 2005). These are summarized below and in Table 2.

Acute mania monotherapy trials

Double-blind trials

One of the earlier trials of risperidone compared with both lithium and haloperidol was conducted by Segal et al (1998). This was a small, double-blind, randomized trial where 45 patients were randomized to either risperidone (n = 15), or lithium (n = 15), or haloperidol (n = 15) for 28 days. The dosage regimen included risperidone 6 mg/day, haloperidol 10 mg/day, and lithium 400 mg twice daily, with lithium levels ranging between 0.6 and 1.2 mmol/L. The Young Mania Rating Scale (YMRS) was the primary outcome measure for efficacy and Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), and Global Assessment of Function (GAF) were the secondary measures. Safety measures included assessment of extrapyramidal symptoms (EPS) by the Simpson Angus Scale (SAS).

Table 2 Double-blind trials of risperidone in bipolar disorder

Authors	Study phase	Number of subjects	Duration	Efficacy results
Segal et al (1998)	mania: monotherapy	45	28 days	risperidone = haloperidol = lithium
Sachs et al (2002)	mania: mixed combination with mood stabilizer	156	3 weeks	risperidone, haloperidol > placebo
Yatham et al (2003)	mania: mixed combination with mood stabilizer	151	3 weeks	risperidone = placebo excluding carbamazepine group risperidone + mood stabilizer > mood stabilizer alone
Hirschfeld et al (2004)	mania: monotherapy	259	3 weeks	risperidone > placebo
Petrie et al (2004)	mania: mixed combination with mood stabilizer	37	8 weeks	risperidone = olanzapine
Khanna et al (2005)	mania: mixed monotherapy	290	3 weeks	risperidone > placebo
Smulevich et al (2005)	mania: mixed monotherapy	438	3 weeks[a]	risperidone > placebo

Adapted from Sajatovic M, Madhusoodanan S, Fuller MA, et al. 2005. Risperidone for bipolar disorders. *Expert Rev Neurother*, 5:177–87. Copyright © 2005, with permission from Future Drugs Ltd.
[a] 3-week placebo controlled followed by 9-week double-blind risperidone vs haloperidol.

Comparable improvement was noted in this trial in all 3 groups on the total score for all rating scales at endpoint (BPRS: lithium 9.1; haloperidol 4.9; risperidone 6.5; $F = 1.01$; $df = 2$; $p = 0.37$; YMRS: lithium 15.7; haloperidol 10.2; risperidone 12.4; $F=1.07$; $df = 2$; $p = 0.35$ [analysis of variance]). Similar improvements were noted in the GAF and CGI (Segal et al 1998).

A pivotal double-blind trial on bipolar mania was conducted by Hirschfeld et al (2004). This 3-week, multicenter, double-blind, placebo-controlled, parallel group study assessed the efficacy and safety of risperidone in acute bipolar mania. Inclusion criteria included patients aged 18 or older with a baseline YMRS score of 20 or over and Montgomery Asberg Depression Rating Scale (MADRS) score of 20 or less. Study subjects were randomized to either 1–6 mg/day flexible dose of risperidone (n = 134) or placebo (n = 125). Change in mean total YMRS scores from baseline to endpoint was the primary efficacy measure and changes in scores on the CGI (severity), MADRS, GAS, and Positive and Negative Syndrome Scale (PANSS) were the secondary measures. The mean modal dose of risperidone was 4.1 ± 0.1 mg/day and the maximum dose allowed was 6 mg/day. Within the risperidone group, 81% used concomitant lorazepam compared with 82% of the placebo group, and 22% used antiparkinson medications compared with 11% of the placebo group. Insufficient response was noted as the most commonly reported reason for discontinuation from the study, occurring in 36% of the placebo group compared with 14% of the risperidone group ($\chi^2 = 16.26$; $df = 1$; $p < 0.001$. There were 8 withdrawals due to adverse events in the risperidone group and 6 withdrawals due to adverse events in the placebo group. In this study, the risperidone group showed statistically significant improvement in the YMRS scores compared with placebo group at endpoint (mean change = −10.6, sd = 9.5 vs −4.8, sd = 9.5), with between-group differences seen as early as 3 days after the start of treatment (change with risperidone: mean = −6.8, sd = 5.8; change with placebo: mean = −4.0, sd = 5.8) and continuing through all time points. The drug–placebo difference at endpoint was 5.8 in this trial, and Cohen's effect size computed from change in baseline YMRS at endpoint was 0.61. Statistically significant differences were also noted in the YMRS scores in the risperidone group vs placebo, when further broken down by patients with psychotic features (−7.9, sd = 9.5 risperidone vs −2.5, sd = 9.5 placebo; $p = 0.02$) and without psychotic features (−11.9, sd = 9.5 risperidone vs −6.0, sd = 9.5 placebo; $p = 0.001$). Significantly greater improvements were also noted in the secondary measures including CGI severity ratings, scores on MADRS, PANSS, and Global Assessment Scale (GAS) in the risperidone group compared with placebo group.

Remission rate (YMRS = ±12 at endpoint) in this trial for the risperidone group was 38% compared with 20% for the placebo group. A post-hoc analysis using remission criteria of YMRS = ≤8 showed a rate of 20% for the risperidone group and 9% for the placebo group.

Khanna et al (2005) conducted a 3-week, randomized, double-blind, placebo-controlled trial of risperidone in 290 patients (age 18–65 years) with bipolar I disorder with current manic or mixed episode. The inclusion criteria

included a baseline YMRS score of ≥20. The primary efficacy measure was a change in the mean YMRS total scores from baseline to endpoint. The secondary measures included scores on the CGI, PANSS, MADRS, and GAS. Among the risperidone-treated patients, 89% completed the trial and 71% of the placebo-treated patients completed the trial. Insufficient response (5% risperidone and 15% placebo) was the most common reason for discontinuation. The dropout rate due to adverse effects for the risperidone group was 3% and for the placebo group was 2%. Study subjects received flexible doses of risperidone (1–6 mg/day) or placebo. The mean modal dose of risperidone was 5.6 mg/day. The risperidone group included 146 subjects and the placebo group 144. Their mean baseline YMRS score was 37.2 (se = 0.5). Risperidone showed significantly greater improvement compared with placebo at weeks 1 and 2 and at endpoint (total YMRS; $p < 0.01$). EPS were the most frequently reported adverse events in the risperidone group. This study concluded that in patients with severe manic symptoms, risperidone significantly improved YMRS scores as early as week 1 with substantial changes at endpoint and treatment was well tolerated.

A separate analysis of the above study group was conducted by Gopal et al (2005) to assess the rates of symptomatic remission in patients with bipolar mania receiving risperidone or placebo. Remission was defined as achieving and maintaining a YMRS score ≤8 for the remainder of the trial (usually in bipolar trials a responder is defined as having a ≥50% decrease in YMRS scores from baseline to endpoint). Results of this study showed that 42% of patients in the risperidone group and 13% in the placebo group achieved remission. The odds of remission for patients receiving risperidone were 5.6 (95% confidence interval [CI] = 3.0–10.4; $\chi^2 = 29.9$, $p < 0.0001$), after adjusting for psychosis, baseline YMRS score, sex, number of mood cycles in the previous year, and treatment. The adjusted hazard of remission for the risperidone patients was 4.0 (95% CI = 2.3–6.8; $\chi^2 = 25.9$, $p < 0.0001$). It was concluded that a significant proportion of acutely manic patients receiving risperidone monotherapy achieved symptomatic remission within 3 weeks.

An international, multicenter, randomized, double-blind trial was conducted by Smulevich et al (2005), in which patients with acute bipolar type I mania received 1–6 mg/day risperidone, 2–12 mg/day haloperidol, or placebo for 3 weeks followed by double-blind risperidone or haloperidol for 9 weeks. Placebo-treated patients were crossed over to active treatment. Primary outcome measure was the YMRS score at baseline and weekly for the first 4 weeks, then every other week for the duration of the study. The secondary measures included the CGI, MADRS, BPRS, and GAS. Safety measures included assessment of EPS using the Extrapyramidal Symptom Rating Scale (ESRS). The total number of study subjects was 438 with 154 randomized to risperidone, 144 to haloperidol, and 140 to placebo. The initial 3 weeks of double-blind phase of treatment was completed by 137 (89%) of the risperidone group, 130 (90%) of the haloperidol group, and 119 (85%) of the placebo group. The total 12-week, double-blind treatment was completed by 86% (77/90) of patients treated with risperidone and 88% (56/64) of those treated with haloperidol. The mean ± sd modal dose of risperidone was 4.2 ± 1.7 and haloperidol 8.0 ± 3.6 during the initial 3-week phase, and 4.1 ± 1.8 and 7.4 ± 3.7 mg/day during the 12-week period. Significantly greater reduction from baseline in YMRS scores were seen in risperidone-treated patients compared with the placebo group. Differences between risperidone and haloperidol on the YMRS scores were not significant. At the end of 3 weeks of treatment, more patients were treatment responders (≥ 50% reduction in YMRS score) among the risperidone group (48%) or haloperidol group (47%) than placebo (33%). The difference between risperidone and placebo was significant ($p < 0.01$)

During the 9-week continuation phase, further significant reductions from baseline in YMRS total scores were seen in both double-blind continuation treatment groups. Mean changes from baseline on the YMRS scores for patients who completed the 12 weeks of double-blind treatment were −28.7 for the risperidone group (n = 76) and −7.3 for the haloperidol group (n = 55). An additional 83% of the risperidone group and 89% of the haloperidol group, who did not reach a reduction of over 50% in the YMRS total score at 3 weeks, but continued on double-blind treatment, were responders at 12 weeks. Greater improvements in CGI-Severity scores were seen in both active treatment groups compared with placebo, as early as week 1 and continuing throughout to weeks 3 and 12. The endpoint MADRS scores at 12 weeks in the risperidone and haloperidol groups were similar (4.0 for risperidone and 4.4 for haloperidol). BPRS scores also showed reductions in both active treatment groups at 12 weeks.

The adverse events reported in this study were mild to moderate in severity. At week 3, mean changes from baseline in ESRS total scores were significantly different in the haloperidol group ($p < 0.011$), but not in the risperidone group ($p < 0.051$). At week 12, mean increases in ESRS total

scores were significantly greater with haloperidol than with risperidone ($p < 0.001$). Mean increase in weight (± sd) at 12 weeks study endpoint was 1.4 ± 4.6 for the risperidone group, and 0.8 ± 3.5 in the haloperidol group. During the 3-week initial phase there were 4 withdrawals due to adverse effects in the risperidone group, 3 in the haloperidol group, and 5 in the placebo group. During weeks 4–12 in this trial, there were 6 withdrawals due to adverse effects in the risperidone group and 5 in the haloperidol group. In summary, randomized, controlled trials demonstrate that risperidone is efficacious and relatively well tolerated in the treatment of bipolar mania (Table 1). A limitation of the large trials by Hirschfeld et al (2004) and by Khanna et al (2005) is the short (3-week) duration. This somewhat limits extrapolation of results interpretation to outcomes, particularly longer-term tolerability issues that could be expected in clinical practice. However, the large trial by Smulevich et al (2005) was followed by a 9-week, double-blind risperidone vs haloperidol phase, and these data are perhaps of greatest interest to practitioners caring for patients with bipolar disorder over the long term.

Open-label trials

Hirschfeld et al (2003) conducted a 9-week, open-label extension of the 3-week, placebo-controlled, monotherapy trial in bipolar mania patients discussed earlier in this section. In this extension phase, risperidone was initiated at 3 mg/day and dosed as needed thereafter. Primary efficacy measure was the YMRS. Safety measures included the ESRS for assessment of the EPS. A total of 60% completed the study. The mean modal dose of risperidone was 3.5 mg/day.

Within-group improvements from baseline of the open-label study to the endpoint were statistically significant in both groups who had received placebo and those who had received risperidone in the double-blind phase of the study. ESRS median scores were unchanged at zero from baseline to endpoint in both groups. There was no significant change in mean body weight from baseline (87.2) to endpoint (87.4) in the open-label extension phase.

Vieta et al (2001) conducted an open-label, multi-center, 6-month study of risperidone monotherapy in 96 patients with acute bipolar mania. The efficacy measures included YMRS, PANSS, and CGI. Highly significant improvements ($p < 0.0001$) were noted on all efficacy measures over the study period. EPS increased significantly by week 4 ($p < 0.015$) and decreased by study endpoint ($p < 0.027$). The mean depression ratings as assessed by the Hamilton Depression Rating Scale (HAM-D) improved over the 6-month period ($p < 0.00001$), while exacerbation of mania occurred in 4 patients (4.2%). The mean dose of risperidone in this study was 4.2 mg/day. Weight increase was noted in 13 patients (2.6%). Three patients (0.6%) withdrew from the study secondary to weight increase.

Combination therapy trials

Double-blind trials

One of the earlier trials was conducted by Sachs et al (2002) to evaluate the efficacy and safety of risperidone as an adjunctive therapy to mood stabilizers in bipolar patients experiencing a manic or mixed episode. The YMRS was the primary efficacy measure and the BPRS and CGI the secondary measures. The inclusion criteria included patients' age (18–65 years) and YMRS score of ≥ 20. Out of the 156 patients, 51 were randomized to placebo, 52 to flexible dose of risperidone (1–6 mg/day), and 53 to flexible dose of haloperidol (2–12 mg/day) in addition to mood stabilizers (lithium or divalproex) for up to 3 weeks after a washout period of 3 days.

Significant improvements in the YMRS and CGI scores were noted in both the active treatment groups: risperidone (−14.3) and haloperidol (−13.4) compared with placebo (−8.2). Patients with or without psychotic features in both the risperidone and haloperidol groups showed significant improvement.

Treatment discontinuation rate in this study for placebo plus mood stabilizer group was 49%, risperidone plus mood stabilizer group 28%, and the haloperidol plus mood stabilizer group 53%. Mean modal dose of risperidone was 3.8 mg/day and of haloperidol 6.2 mg/day; 8% of the placebo group, 17% of the risperidone group, and 38% of the haloperidol group of patients received antiparkinson medications. The between-group difference in the use of antiparkinson medications was significant for the haloperidol group compared with the placebo group (Cochran-Mantel-Haenszel $\chi^2 = 12.96$, $df = 1$, $p = 0.001$).

A larger, double-blind, randomized, placebo-controlled 3-week study was conducted by Yatham et al (2003) to assess the efficacy and safety of risperidone as adjunct therapy to mood stabilizers (lithium, divalproex, or carbamazepine) in bipolar I disorder, manic or mixed episode. Inclusion criteria included hospitalized patients aged 18–65 years with a baseline YMRS score of ≥ 20 receiving a mood stabilizer. Out of the 151 patients who were randomized and started on study medication, 75 received risperidone flexible doses

(1–6 mg/day) and 76 placebo. The primary efficacy measure was the change from baseline in the YMRS score. Other measures included YMRS, CGI, BPRS, and a 21-item HAM-D. Assessments were done at baseline, weekly intervals, and endpoint.

Statistically significant improvement was not seen in the risperidone group compared with placebo, even though the YMRS scores improved in the risperidone group. However, a post-hoc analysis excluding the carbamazepine subgroup found that YMRS changes were significantly greater in the risperidone plus mood stabilizer group at endpoint. In the subgroup that excluded recipients of concomitant carbamazepine, change from baseline YMRS for risperidone-treated patients was −15.2 compared with −9.8 in placebo-treated patients ($p < 0.05$). Endpoint plasma concentrations of risperidone and/or risperidone plus 9-hydroxyrisperidone (normalized for the median 4 mg risperidone dosage) in the subgroup patients were approximately 40% lower than in other risperidone-treated patients. Treatment discontinuation rates and adverse event incidence were similar in both groups in this trial.The mean modal dose of risperidone was 4 mg/day. The most frequently reported adverse events included EPS (21.3% in risperidone group vs 8% in placebo group), headache (9% in each group), insomnia (4% vs 8%), and nausea (5% vs 3%). The mean weight change from baseline to endpoint was +1.7 kg for the risperidone group and +0.5 kg for the placebo group ($p = 0.012$). No clinically significant changes in laboratory values were observed in either group. No specific information regarding blood sugar–lipid changes are reported is the trial.

A small 8-week, double-blind, adjunctive trial of risperidone was conducted by Petrie (2004) comparing risperidone ($n = 16$) and olanzapine ($n = 21$) in 37 patients with bipolar mania, who were on mood stabilizers (lithium or divalproex). The primary outcome measure was the YMRS and secondary measures included the BPRS, CGI, and HAM-D. EPS was assessed by the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Scale (BAS), and the SAS. Ten out of 16 risperidone patients and 14 out of 21 olanzapine patients completed this 8-week trial. Similar improvements were noted on all efficacy measures in both groups at study endpoint. EPS ratings were minimal in both groups. Mean weight gain was significantly greater ($p < 0.05$) in the olanzapine group (3.6 kg) compared with the risperidone group (0.87 kg).

In summary, randomized, controlled combination trials demonstrate that risperidone augmentation is efficacious and relatively well tolerated for treatment of patients with bipolar mania. Trials by Sachs et al (2002) and by Yatham et al (2003) were large studies involving more than 250 patients. As with monotherapy trials, the 3-week duration of the largest trials somewhat limit interpretation of tolerability findings as they relate to clinical practice settings. However, as most bipolar patients in a clinical setting are likely to receive treatment with more than one medication, tolerability and dosing results from large, combination-therapy trials may be particularly relevant to a clinical practice setting.

Open-label trials

A large open-label, multi-center, 6-week study was conducted by Vieta et al (2002) to assess the efficacy and safety of risperidone as adjunctive therapy to mood stabilizers in 174 patients with bipolar disorder, experiencing a manic (YMRS score > 20), hypomanic (YMRS > 7), or mixed episode (YMRS > 7). The efficacy measures included the YMRS, PANSS, HAM-D, and CGI. The safety measures included the Udvalg for Kliniske Undersogelser (UKU) scale for EPS. Out of the 159 patients who completed the study, 10% received risperidone monotherapy, 42% risperidone in combination with lithium, 16% risperidone in combination with lithium and another mood stabilizer, 23% risperidone in combination with carbamazepine, and 12% risperidone in combination with valproate. Four patients discontinued the study due to lack of response, 4 due to side-effects, 2 due to withdrawal of consent, and 3 were lost to follow-up.

Significant improvements were noted in the YMRS and HAM-D scores over the 6-week study period ($p < 0.0001$) and in PANSS over first the 4 weeks of study ($p < 0.0001$). The CGI ratings improved in 22.5% of patients. No significant difference was noted in the EPS ratings as measured by UKU at baseline and week 4. The adverse events reported include EPS, drowsiness, weight gain, dry mouth, impotence, dizziness, weight loss, hypotension, and impaired concentration and amenorrhea.

In a 12-week study of risperidone added on to mood stabilizers in 108 patients with bipolar mania, Yatham et al (2003) found significant decreases in YMRS scores from baseline to week 1 (−10.8, $p < 0.0001$), continuing through to week 3 (−17.1, $p < 0.0001$) and week 12 (−22.6, $p < 0.0001$). 32% of patients responded to risperidone treatment (defined as ≥ 50% reduction in YMRS) at week 1, 68% at week 3, and 90% at week 12. Significant decreases in HAM-D scores from baseline to endpoint were also noted. No significant changes in EPS were noted during the study

duration. The mean daily dose of risperidone was 2 mg/day. It is of interest that the dose of risperidone in this study was relatively low compared with that in some other trials, possibly because risperidone therapy was used as an add-on to mood stabilizers in this instance.

Bowden et al (2004) conducted a 10-week, open-label. continuation phase from a 3-week combination treatment trial (lithium or valproate plus placebo, risperidone or haloperidol). Out of 156 patients enrolled in the 3-week study, 85 entered the open-label extension phase and 48 completed the 10-week endpoint. Significant improvements were noted compared with placebo ($p < 0.001$) in the YMRS scores in risperidone-treated patients at the conclusion of the double-blind phase and the 10-week open-label phase. Symptom remission (YMRS ≤ 12) was seen in 38 patients at the end of the 10-week study.

The BPRS, CGI, and HAM-D scores also showed significant improvement ($p < 0.05$) during both phases of the study. Treatment was well tolerated and modest weight gain was noted.

Longer-term bipolar trials

A 6-month, open-label, multi-center study by Vieta et al (2001) compared the efficacy and safety of risperidone in bipolar manic (YMRS ≥ 20), hypomanic (YMRS ≥ 7), depressed (HAM-D > 7), or mixed (YMRS ≥ 7) episodes or schizoaffective disorder. The reduction in YMRS scores from baseline to endpoint was the primary efficacy measure. Secondary measures included the HAM-D, PANSS, and CGI. EPS was assessed by the UKU scale. The mean dose of risperidone at baseline was 4 mg/day and at 6 months 3.9 mg/day. A total of 430 patients completed the study. Patients who received addition of risperidone showed highly significant improvements ($p < 0.0001$) on the YMRS and HAM-D at both 6 weeks and 6 months, and on the CGI and PANSS at both 4 weeks and 6 months. The most frequently reported adverse events were motor side-effects and weight gain. Significant improvement ($p < 0.0001$) was noted in the mean UKU scores from baseline to endpoint. No new cases of tardive dyskinesia were observed during the study period.

While open-label studies, including longer trials such as the study by Vieta et al (2001), do not provide comparative data in terms of efficacy and tolerability, tolerability findings and dosing in these longer-term, outpatient trials may be particularly relevant to a clinical practice setting.

Geriatric and child populations

Elderly

Psychopharmacological treatment of the elderly patient with bipolar disorder is complicated by the various pharmacokinetic and pharmacodynamic vulnerabilities of the elderly, concurrent medications, and concomitant medical conditions. Renal clearance of risperidone and its active metabolite 9-hydroxy risperidone are decreased in the elderly and the elimination half-lives are prolonged. The expert consensus guideline series on the treatment of Bipolar Disorder (Keck et al 2004) recommend risperidone as the preferred (first-line) atypical antipsychotic agent along with quetiapine as a first-line agent for the treatment of bipolar disorder in the elderly. There are no controlled studies of risperidone for bipolar disorder in the elderly. Anecdotal case reports and retrospective reviews (Sajatovic 1996) indicate clinical improvement and moderate tolerability with risperidone in bipolar patients, but data interpretation is limited by the small sample size of these reports. Controlled studies with larger sample size are required to further investigate the use of risperidone in the elderly bipolar patients.

Children

None of the atypical antipsychotics are approved by the FDA for treatment of bipolar disorder in children or adolescents. However, recent guidelines have been developed that address the diagnosis, comorbidity, acute treatment, and maintenance treatment of bipolar disorder in children and adolescents (Kowatch et al 2005). The guidelines by Kowatch and colleagues (2005) note that monotherapy with traditional mood stabilizers such as lithium, divalproex, and carbamazepine as well as the atypical antipsychotic compounds olanzapine, risperidone, and quetiapine are determined to be first-line treatments for bipolar disorder I manic or mixed presentation in children–adolescent populations. The expert consensus guidelines (Keck et al 2004) do not identify any specific atypical antipsychotic as first-line treatment for bipolar disorder in adolescents. Risperidone is recommended as high second-line treatment along with other atypical antipsychotics except clozapine.

Biederman (2003) conducted an open-label, 8-week study of risperidone in 30 outpatient children and adolescents aged 6–17 years with bipolar disorder. The inclusion criteria included a YMRS score of ≥ 15. The dose range for children up to 12 years of age was 0.25–2 mg/day; for older adolescents, the dose range was 0.5–4 mg/day. The

YMRS scores improved significantly from baseline to endpoint.

Frazier et al (1999) conducted a retrospective study of risperidone in 28 children and young adolescents with bipolar disorder. The mean dose of risperidone was 1.7 mg and mean duration of treatment 6.1 months. Response was assessed by CGI-Improvement Scale and was achieved by 82% of patients. Weight gain, somnolence, and sialorrea were the common adverse events.

As in the case of the elderly, data are limited on the use of risperidone in bipolar disorder in children and adolescents. Controlled, well-designed studies are needed to further investigate the role of risperidone in bipolar disorder in children.

Safety and tolerability issues

Common adverse events

Based upon results of controlled studies of risperidone therapy in bipolar mania, risperidone was generally well tolerated both when used as monotherapy and in combination therapy with mood-stabilizing compounds. Percentages of patients who discontinued controlled-study participation due to side-effects was not greater compared with placebo (Fenton and Scott 2005; Sajatovic et al 2005). In the RCT reported by Hirschfeld et al (2004) adverse events occurring in >10% of bipolar patients included somnolence, headache, hyperkinesia, dyspepsia, and nausea. Somnolence was the most common adverse event reported among risperidone-treated patients (28%). The total scores for ESRS were significantly greater in the risperidone than the placebo group. However, the subscales for Parkinsonism, dystonia, and dyskinesia did not show any significant differences at endpoint between the groups. Mean weight gain vs placebo was generally significant, ranging from 0.3 to 2.4 kg, in most randomized, controlled trials (Sachs et al 2002; Hirschfeld et al 2004; Smulevich et al 2005). However, in the trial by Khanna et al (2005), mean body weight changes from baseline to endpoint were +0.1 kg in both groups.

Manic reaction did not occur with increased frequency in risperidone-treated compared with placebo-treated patients (Sachs et al 2002; Hirschfeld et al 2004; Smulevich et al 2005), and Hirschfeld et al (2004) reported no evidence of treatment-emergent depression associated with risperidone therapy. Rare adverse effects reported in open-label trials of risperidone therapy (adjunct or combination) included seizures in two individuals (Bahk et al 2004), and single-case reports of neuroleptic malignant syndrome, dysuria, dyskinesia, and confusion (Bahk et al 2004; Bowden et al 2004; Vieta et al 2004). An open-label trial by Vieta et al (2004) noted study withdrawal in four individuals treated with risperidone for adverse effects that included akathisia, impotence, drowsiness, and weight gain. There were no cases of clinically relevant QT interval prolongation noted with risperidone therapy (Sachs et al 2002; Khanna et al 2003; Yatham et al 2003; Hirschfeld et al 2004; Smulevich et al 2005). Finally, serious cerbrovascular events, and increased rate of fatalities have occurred in elderly patients with dementia and behavioral disturbances who received risperidone therapy compared with placebo, although this has not been documented in individuals treated for bipolar mania (FDA 2005).

Extrapyramidal symptoms

Risperidone therapy has been associated with increased rates of extrapyramidal side-effects compared with placebo based upon controlled studies. Rates of extrapyramidal symptoms seen with risperidone therapy are lower than rates seen with haloperidol. Although extrapyramidal disorder was the most common adverse event in the monotherapy study by Smulevich et al (2005), the rate was relatively low; 17% for risperidone compared with a rate of 40% in the haloperidol group at the 3-week point in the study. In a 6-month, open-label study (Vieta et al 2004), extrapyramidal symptoms associated with risperidone were noted to be dose-dependent. Symptoms were greater when risperidone dosage was 4.5 mg/day, but decreased significantly ($p = 0.027$) when dosage was decreased to 3 mg/day by the end of the trial (Vieta et al 2004). Given the dose relationship between extrapyramidal symptoms and risperidone, determination of lowest effective dosing is critical in achieving medication level that will balance the need for antipsychotic efficacy and tolerability.

Metabolic concerns

As requested by the FDA, all manufacturers of atypical antipsychotics have revised the labeling for their atypical antipsychotic to highlight the potential for diabetes (Janssen 2003b). This information has been summarized by a Consensus Panel (ADA 2004). Severe hyperglycemia, including ketosis, has been documented in patients receiving this class of medications. Clozapine and olanzapine have been most clearly associated with these effects, while risperidone and quetiapine have produced discrepant results. Aripiprazole and ziprasidone are associated with little or no diabetes, but have not been used as extensively as the

other agents implicated and therefore the exact risk is unknown.

In short-term risperidone therapy trials modest weight gain has been noted. In a 3-week, risperidone monotherapy trial (Hirschfeld et al 2004), mean body weight changes were 1.6 kg (sd 2.2) in risperidone-treated patients and −0.25 kg (sd 2.4) in placebo-treated patients ($t = 6.47$, $df = 225$, $p < 0.001$). In a 3-week, combination therapy, acute mania treatment trial (Sachs et al 2002), weight gain in risperidone plus mood-stabilizer-treated patients was significantly greater than in patients treated with mood stabilizer plus placebo ($t = 2.95$, $df = 105$, $p < 0.004$). However, risperidone may be associated with clinically significant weight gain in some patients, particularly when prescribed over a longer time period and with concomitant traditional mood-stabilizing medication. Yatham et al (2003) reported clinically significant weight gain (more than 7%) in 21% of individuals receiving adjunctive mood stabilizers over 12 weeks, while Vieta et al (2004) reported significant weight gain in 9.4% of individuals on risperidone monotherapy over a 6-month time period.

Risperidone may be associated with impaired glucose tolerance or diabetes mellitus (Newcomer et al 2002; ADA 2004). A prospective, randomized, double-blind, 14-week trial (Lindenmayer et al 2003) assessed the effects of clozapine, olanzapine, risperidone, and haloperidol on glucose and cholesterol levels in hospitalized patients with schizophrenia or schizoaffective disorder ($n = 108$). The mean glucose levels were obtained at the end of an 8-week, fixed-dose period and a 6-week, variable-dose period. Increases in glucose levels were highest for olanzapine, followed by clozapine and risperidone. In the study by Lindenmayer and colleagues (2003), 14 out of 101 patients developed abnormal glucose levels (> 125 mg/dL) during the trial (6 with clozapine, 4 with olanzapine, 3 with risperidone, and 1 with haloperidol).

Patients treated with an atypical antipsychotic medication and in particular those with established diabetes (or with risk factors such as a family history or obesity) should be monitored closely for changes in weight, lipids, and glucose control. Monitoring of these parameters at the beginning of therapy and periodic monitoring during therapy are recommended (ADA 2004).

As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels. In a 3-week, double-blind, placebo-controlled trial (Hirschfeld et al 2004) for risperidone-treated patients, the mean plasma prolactin levels increased from 13.7 ng/mL (sd = 9.8) to 43.5 ng/mL (sd = 23.0) in men, and from 19.4 ng/mL (sd = 26.6) to 96.1 ng/mL (sd = 51.4) in women. In this 3-week trial, there was no correlation with adverse events for hyperprolactinemia. However, in a 12-week trial, prolactin-related adverse effects including decreased libido and abnormal sexual function, nonpuerperal lactation, breast pain, and dysmenorrhea occurred in 4% of risperidone-treated and 1% of haloperidol-treated patients (Smulevich 2005). Prolactin-related adverse effects may occur in both men and women, and should be assessed in patients on risperidone. As is the case with extrapyramidal symptoms, prolactin effects with risperidone may be minimized by establishing lowest effective dosing.

In summary, risperidone appears relatively well tolerated in bipolar manic patients. In clinical settings weight gain and metabolic concerns may be less with risperidone than with some atypical antipsychotic compounds such as olanzapine and clozapine, while sedation and orthostasis may be less problematic with risperidone than with compounds such as quetiapine (Fuller and Sajatovic 2005). In contrast, extrapyramidal symptoms may be a greater concern with risperidone compared with some atypicals such as olanzapine and quetiapine (Fuller and Sajatovic 2005).

Dosage and administration

Recommended dosing of risperidone in bipolar mania is 2–3 mg once daily. In more severely ill hospitalized patients such as those included in pivotal trials higher doses may sometimes be required. If needed, this may be adjusted by 1 mg/day in intervals of approximately 1 day. Suggested dosing range is 1–6 mg/day in healthy individuals (Fuller and Sajatovic 2005). In the elderly, a starting dose of 0.25–1 mg in 1–2 divided doses is recommended, with slow titration if needed. If once-daily dosing in elderly or debilitated individuals is considered, a twice-daily regimen should be used to titrate to target dose, and this dose maintained for 2–3 days prior to switching to once-daily dosing. Children and adolescents with bipolar mania may be treated with an initial dose of 0.5 mg, and gradually titrated to 0.5–3.0 mg/day (Fuller and Sajatovic 2005).

Dosing adjustment for renal impairment is suggested, as clearance of the active moiety of risperidone is decreased by 60% in individuals with moderate to severe renal disease (Fuller and Sajatovic 2005). Dosing may also need adjustment in those with hepatic dysfunction, as it has been noted that mean fraction of risperidone in plasma was

increased by 35% in individuals with hepatic impairment compared with healthy subjects (Fuller and Sajatovic 2005).

Conclusions

Risperidone is an atypical antipsychotic medication with demonstrated efficacy and relatively good tolerability in the treatment of patients with acute bipolar mania. Current practice guidelines for bipolar disorder support the use of atypical antipsychotic medications as monotherapy or as a component of polytherapy–cotherapy. While findings from randomized, controlled, monotherapy trials are clearly important, in clinical settings polytherapy for bipolar disorder is much more common than monotherapy.

In clinical practice settings, risperidone is widely utilized to treat acute mania, often in conjunction with traditional mood stabilizers such as lithium or valproate, and is often subsequently utilized as part of a longer-term medication treatment regimen. As with any drug treatment, medication selection ideally involves an analysis of demographic factors, including family and personal history of response to a particular agent as well as attention to potential side-effects and drug interactions. Unfortunately, as demonstrated in our review, most controlled studies of bipolar mania are of relatively limited duration and with research populations that do not necessarily represent the majority of clinical bipolar populations. Large-scale, multi-center studies that examine the longitudinal course of bipolar disorder and the effectiveness of current treatments in diverse populations and using all or most available treatments such as the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study will be an important future source of information in helping clinicians to determine best treatments for individual patients with bipolar disorder (Kogan et al 2004; Sachs et al 2004).

Disclosures

There was no financial or editorial support provided to the authors for writing this manuscript. Dr Sajatovic receives grant support from Bristol-Myers Squibb and Abbott Laboratories, is a consultant to GlaxoSmithKline and AstraZeneca, and is on the Speakers Bureau for AstraZeneca and Bristol-Myers Squibb. Dr Madhusoodananon is a consultant and on the Speakers Bureau for AstraZeneca and Bristol-Myers Squibb. He has received research honoraria for clinical drug trials from Janssen, Eli Lilly, AstraZeneca, Pfizer, and Bayer Pharmaceutical. Dr Fuller is on the Speaker's Bureau for Janssen.

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