Current PSYCHIATRY

Risperidone's 2 new pediatric indications

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Risperidone is the first second-generation antipsychotic (SGA) to receive FDA approval for treating children and adolescents with bipolar mania or schizophrenia. Specifically, the SGA is indicated for treating schizophrenia in patients age 13 to 17 and as monotherapy in short-term treatment of manic or mixed episodes of bipolar I disorder in patients age 10 to 17 (*Table 1*).

Risperidone also is approved for:

- schizophrenia in adults
- acute mania or mixed episodes associated with bipolar I disorder in adults, alone or in combination with lithium or valproate
- irritability associated with autistic disorder in patients age 5 to 16.

Table 1

Risperidone: Fast facts

Brand name: Risperdal
Class: Second-generation antipsychotic
New indications: Schizophrenia in adolescents age 13 to 17 and monotherapy in short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents age 10 to 17. (Risperidone had been approved for schizophrenia and short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and treatment of irritability associated with autistic disorder in children and adolescents.)
Approval date: August 22, 2007 for pediatric schizophrenia and mania indications
Manufacturer: Janssen, L.P.
Dosing forms: 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets; 0.5-, 1-, 2-, 3-, and 4-mg orally disintegrating tablets; 1 mg/mL oral solution
Recommended target dosage: 3 mg/d (pediatric schizophrenia) or 2.5 mg/d (pediatric bipolar mania). See *Table 2 (page 21)* for initial dosages and titration

Approval supports antipsychotic use in children with schizophrenia or bipolar disorder

Clinical implications

Risperidone is widely used off-label to treat irritability in children with pervasive developmental disorders,[1,2] aggressive behaviors associated with conduct disorder,[3] psychotic disorders,[4] and bipolar disorder.[5] It also has been used off-label to treat pediatric schizophrenia and bipolar disorder for many years.

These 2 new indications give clinicians additional support for using SGAs in children and adolescents with these serious psychiatric disorders.

How it works

Risperidone's therapeutic activity in schizophrenia seems to be mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) receptor antagonism. Antagonism at receptors other than D2 and 5HT2 may explain some of risperidone's other therapeutic effects.

Pharmacokinetics

In children, the half-lives of risperidone and its major active metabolite 9-hydroxyrisperidone are 3 ± 2.3 hours and 22 ± 46 hours, respectively.[6] The pharmacologic activity of

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Clinical Point

For pediatric schizophrenia, doses >3 mg/d were no more efficacious than lower doses

9-hydroxyrisperidone is similar to that of risperidone.

Risperidone is extensively metabolized in the liver by the cytochrome P-450 (CYP) 2D6 enzyme system. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by CYP 2D6. Food does not affect the rate or extent of the drug's absorption.[6]

Efficacy studies

In schizophrenia. Approval of the indication for pediatric schizophrenia was based on data from 2 short-term (6 and 8 weeks) randomized, double-blind, controlled trials involving a total of 416 patients age 13 to 17 who met DSM-IV-TR criteria for schizophrenia and were experiencing an acute episode at enrollment.[7] In one study, patients received risperidone, 1 to 3 mg/d, 4 to 6 mg/d, or placebo. In the other study, dosages were 0.15 to 0.6 mg/d or 1.5 to 6 mg/d. Except for patients in the 0.15 to 0.6 mg group (who initially received 0.05 mg/d), most patients started risperidone at 0.5 mg/d. In both trials, starting dosages were titrated to the target range in approximately 7 days.

Outcomes were measured as changes in total Positive and Negative Syndrome Scale (PANSS) and Personal and Social Performance (PSP) scale scores. The multi-item PANSS inventory measures positive and negative schizophrenia symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. The PSP gauges personal and social functioning in socially useful activities (work and study), personal and social relationships, self-care, and disturbing/aggressive behaviors.

Risperidone, 1 to 6 mg/d, improved schizophrenia symptoms significantly more than placebo, as measured by PANSS scores. Doses >3 mg/d did not show greater efficacy than lower doses, as evaluated by PANSS and PSP scores.

Adverse reactions experienced by >5% of patients treated with risperidone included somnolence, parkinsonism, tremor, dystonia, dizziness, akathisia, increased salivation, and anxiety.[7]

In bipolar I disorder. Risperidone's efficacy for short-term treatment of mania in children and adolescents was demonstrated in a 3-week, randomized, double-blind, placebo-controlled, multi-center study of 169 patients age 10 to 17 who were experiencing a manic or mixed episode of bipolar I disorder.[7] Patients were randomly assigned to risperidone, 0.5 to 2.5 mg/d or 3 to 6 mg/d, or placebo. All patients were started at 0.5 mg/d and this dose was titrated to the target dosage range in 7 days.

Risperidone, 0.5 to 6 mg/d, significantly decreased the total Young Mania Rating Scale score—a measure of the severity of elevated mood, increased motor activity energy, sexual interest, sleep, irritability, speech (rate/amount), language (thought disorder, content, disruptive), aggressive behavior, appearance, and insight. No evidence of increased efficacy was observed at doses >2.5 mg/d. In this trial, symptoms reported by >5% of patients included fatigue, dizziness, dystonia, parkinsonism, akathisia, abdominal pain, dyspepsia, nausea, vomiting, and diarrhea.[7]

Pediatric dosing. Based on these studies, the recommended starting dose for children and adolescents is 0.5 mg/d, with titration in 0.5- to 1-mg increments to targets of:

- 3 mg/d for schizophrenia
- 2.5 mg/d for bipolar mania (***Table 2***).[7]

Tolerability studies

In long-term studies, the most commonly reported adverse events associated with risperidone in children and adolescents have been rhinitis, abdominal pain, increased saliva, body pain, gynecomastia, and weight increase.[8] Specific adverse effects that pose long-term concerns are:

- tardive dyskinesia (TD)
- weight gain
- increased prolactin levels.

Tardive dyskinesia. In clinical trials that included 1,885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone,

Table 2

Recommended dosing of risperidone for pediatric schizophrenia and bipolar mania

Indication	Initial dose	Titration	Target dose	Effective dose range
Schizophrenia, adolescents age 13 to 17	0.5 mg/d	0.5 to 1 mg/d	3 mg/d	1 to 6 mg/d
Bipolar mania, children and adolescents age 10 to 17	0.5 mg/d	0.5 to 1 mg/d	2.5 mg/d	0.5 to 6 mg/d

Source: Reference 7

2 patients (0.1%) were reported to have TD, which resolved when risperidone was discontinued.[7] To monitor for TD, administer the Abnormal Involuntary Movement Scale at baseline and every 6 months while using risperidone in pediatric patients.

Weight gain. In long-term, open-label trials, patients with autistic or other psychiatric disorders gained an average 7.5 kg after 12 months of risperidone treatment. Most of the weight gain occurred in the first 6 months.[9] Expected normal weight gain in children is 3 to 3.5 kg/year adjusted for age, based on Centers for Disease Control and Prevention normative data.

Follow the American Diabetes Association guidelines[10] for monitoring metabolic parameters during antipsychotic treatment, and intervene if clinically significant weight gain occurs.

In a 16-week, placebo-controlled study,[11] metformin reversed weight gain associated with SGAs in children and adolescents. Metformin's potential side effects include hypoglycemia, diarrhea, nausea/vomiting, and (rarely) lactic acidosis, but no adverse events were attributed to metformin.

Increased prolactin. As in adults, risperidone elevates serum prolactin in children and adolescents. All pediatric risperidone trials—of autism,[2] disruptive behavior disorders in children with subaverage intelligence,[9] schizophrenia,[7] and bipolar mania—have shown increased serum prolactin. Risperidone's long-term effects on growth and sexual maturation have not been fully evaluated, but hyperprolactinemia may inhibit reproductive function.

Findling et al[12] analyzed data from 5 clinical trials (total 700 patients) in which children and adolescents age 5 to 15 years with subaverage IQs and conduct or other disruptive behavior disorders received risperidone for up to 55 weeks. Mean prolactin levels rose from 7.8 ng/mL at baseline to 29.4 ng/mL at weeks 4 to 7, then progressively decreased to 16.1 ng/mL at weeks 40 to 48 (N=358) and 13.0 ng/mL at weeks 52 to 55 (N=42). Girls returned to a mean value within the normal range (≤30 ng/mL) by weeks 8 to 12, and boys were close to normal values (≤18 ng/mL) by weeks 16 to 24.

The researchers concluded that serum prolactin levels in children tend to rise and peak within the first 1 to 2 months of risperidone treatment and then steadily decline to values within or very close to normal range by 3 to 5 months.

The biological significance of chronic, mild prolactin elevations is unknown.[13] Children entering puberty appear to be at highest risk for elevated prolactin and clinical symptoms while treated with risperidone.[14] Therefore, ask all adolescents treated with risperidone about increases in breast size and galactorrhea. Switch those who develop these symptoms to an SGA that does not increase serum prolactin.

Contraindications. Risperidone is contraindicated in patients with a known hypersensitivity to the drug.

Clinical Point

Monitor for tardive dyskinesia with the Abnormal Involuntary Movement Scale at baseline and every 6 months while using risperidone

References

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Related Resource

- Risperdal prescribing information. www.risperdal.com/risperdal/shared/pi/risperdal.pdf.

Drug Brand Names

Lithium • Eskalith, Lithobid	Risperidone • Risperdal
Metformin • Glucophage, Fortamet	Valproate • Depakote

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Clinical Point

Serum prolactin tends to rise in the first 1 to 2 months of risperidone treatment, then declines to near normal range by 3 to 5 months

Bottom Line

Risperidone has been shown to be significantly more effective than placebo for improving schizophrenia symptoms in adolescents and significantly decreases mania symptoms in adolescents with bipolar I disorder. Three concerns with long-term risperidone use in children and adolescents are the risk for tardive dyskinesia, weight gain, and increased prolactin levels.