Risperidone (oral)

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Risperidone belongs to a class of antipsychotic agents, the benzisoxazole derivatives.[1] It is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT_2 and dopaminergic D_2 receptors.[2,3] Risperidone also binds to alpha-1 adrenergic receptors and, with lower affinity, to H_1 histamine and alpha-2 adrenergic receptors. Risperidone has no affinity for cholinergic receptors.

The antipsychotic activity of risperidone is considered to be due to both risperidone and its active metabolite, 9-hydroxyrisperidone. As a potent D_2 antagonist, risperidone improves the positive symptoms of schizophrenia and causes less depression of motor activity and induction of catalepsy than classical neuroleptics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.[1]

Risperidone is available as a tablet formulation in strengths of 0.5 mg, 1 mg, 2 mg, 3 mg or 4 mg.[1,2] An oral solution (1 mg/mL) and a prolonged-release intramuscular injection are also available.[1]

Indications

Risperidone is indicated for the treatment of the following conditions:[2]

- Acute and chronic schizophrenic and related psychoses in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness) or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone alleviates affective symptoms (such as depression, feelings of guilt, anxiety) associated with schizophrenia. In patients who have shown an initial treatment response, risperidone is effective in maintaining the clinical improvement.
- Mania in bipolar disorder. These episodes are characterised by symptoms such as elevated, expansive or irritable mood, inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility or poor judgement, including disruptive or aggressive behaviours.
- Conduct and other disruptive behaviour disorders in children (aged 5–12 years), with sub-average intellectual functioning or mental retardation in whom destructive behaviours (e.g. aggression, impulsivity and self-injurious behaviours) are prominent.

Dosing

Table I outlines the recommended daily doses of risperidone by indication.[2] Risperidone may be given with or without meals.[3,4]

Pharmacokinetics

Risperidone is rapidly and completely absorbed after oral administration, reaching peak plasma concentrations within 1–2 hours.[1–4] The absorption of risperidone is not affected by food.[1,2,4] Risperidone is partly metabolised by CYP2D6 to 9-hydroxyrisperidone, which has a similar pharmacological activity to risperidone. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life for both 9-hydroxyrisperidone and risperidone combined with 9-hydroxyrisperidone is 24 hours.[1] For risperidone, steady state is reached within 1 day in most patients, whereas for 9-hydroxyrisperidone it is reached within 4–5 days of dosing. Risperidone plasma concentrations are dose proportional within the therapeutic dose range.[1,4] The pharmacokinetics of risperidone, 9-hydroxyrisperidone and the active moiety are similar in children and adults.[2] Risperidone Quicklet tablets are bioequivalent to conventional risperidone tablets.[1]

Efficacy

Schizophrenia

Risperidone has a favourable profile with regard to efficacy in the treatment of schizophrenia. Treating schizophrenia with risperidone at the earliest stage possible results in optimal improvement.[5] The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, which included more than 2500 patients who met the DSM-IV criteria for schizophrenia.[3,5] The findings were as follows:

- In a six-week placebo-controlled trial involving titration of risperidone in doses of up to 10 mg/day administered twice daily, the response to risperidone was superior to that of the placebo.
- In an eight-week placebo-controlled trial involving four fixed doses of risperidone (2 mg/day, 6 mg/day, 10 mg/day and 16 mg/day, administered twice daily), the response to all four risperidone groups was superior to that of the placebo.

Table I: Recommended daily doses of risperidone by indication[2]

Indication	Recommended dose
Schizophrenia *Adults*	• May be given once or twice daily. • Recommended starting dose: 2 mg/day. • Dosage may be increased to 4 mg/day on the second day. • Beyond day 2, the dosage may be maintained unchanged or further individualised, if needed. Most patients will benefit from daily doses of between 4 mg and 8 mg. • Doses above 10 mg/day should be considered only if the benefits outweigh the risk. The maximum total daily dose is 16 mg. • Recommended starting dose: 0.5 mg twice daily. • This dosage can be individually adjusted in increments of 0.5 mg twice a day, up to 1–2 mg twice daily. • Not recommended for children under 15 years of age.
Mania in bipolar disorders* *Adults* *Children and adolescents less than 18 years of age*	• To be administered once daily. • Recommended starting dose: 2 mg/day or 3 mg/day. • If indicated, dosage may be adjusted in increments of 1 mg/day, at intervals of not less than 24 hours. • Efficacy was demonstrated in flexible doses over a range of 1–6 mg/day. • Experience is lacking in bipolar mania
Conduct and other disruptive behaviour disorders in children aged 5-12 years* *Subjects <50 kg:* *(Experience is lacking in children under 5 years)*	• Recommended starting dose: 0.01 mg/kg once daily. • If needed, dosage may be individually adjusted in increments of 0.01 mg/kg once a day, but not more frequently than every other day. • Recommended maintenance dose: 0.02–0.04 mg/kg once daily. The mean dose is 0.03 mg/kg once daily.

*Continued use must be evaluated and justified on an ongoing basis.

- In an eight-week dose comparison trial involving five fixed doses of risperidone (1 mg/day, 4 mg/day, 8 mg/day, 12 mg/day and 16 mg/day, administered twice daily), the response to risperidone doses of 4 mg/day, 8 mg/day and 16 mg/day was superior to that of 1 mg/day.
- In a four-week placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 mg/day and 8 mg/day, administered once a day), the response to risperidone was superior in both groups compared to that of the placebo group.[3]

In a longer-term trial, adult outpatients who predominantly met the DSM-IV criteria for schizophrenia and who had been clinically stable on an antipsychotic for at least four weeks were observed for 1–2 years after being randomly assigned to receive haloperidol or risperidone at either 2 mg/day or 8 mg/day. Patients who received risperidone experienced a significantly longer time to relapse over this period than those receiving haloperidol.

Manic episodes in bipolar disorder

Smulevich et al designed a three-week controlled trial in which manic patients received risperidone, haloperidol or a placebo, followed by a double-blind trial of risperidone and haloperidol. The conclusion was that risperidone and haloperidol were similarly effective in the treatment of acute mania. The effect was significant compared with that of the placebo. Risperidone was reported to be safer than haloperidol and long-term efficacy was maintained.[6] The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind placebo-controlled monotherapy studies, which included approximately 820 patients who had bipolar I disorder based on the DSM-IV criteria. In the three studies, risperidone was shown to be significantly superior to the placebo at doses of 1 mg/day to 6 mg/day (starting dose 3 mg/day in two studies and 2 mg/day in the other study).[3]

Risperidone has also been studied as adjunct treatment to lithium, sodium valproate and carbamazepine. In a three-week double-blind, randomised controlled trial, the use of mood stabilisers combined with risperidone or a placebo was studied in the treatment of acute mania. At the study end point, Young mania rating scale (YMRS) scores improved by –14.5 and –10.3 in the risperidone and placebo groups, respectively, although not reaching statistical significance ($P < 0.089$). When risperidone combined with lithium or sodium valproate was compared with a placebo combined with lithium or sodium valproate, YMRS scores improved by –15.2 and –9.8, with the result being statistically significant ($P < 0.047$). In another trial, a double-blind, placebo-controlled comparison was made between haloperidol, risperidone and a placebo combined with a mood stabiliser in patients with acute mania. Significantly greater reductions in YMRS scores were achieved with both haloperidol and risperidone compared with the placebo group.[3,6]

Conduct disorder

The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind, placebo-controlled studies, which included approximately 240 patients of 5–12 years of age and who had been diagnosed with disruptive behaviour disorders and borderline intellectual functioning or mild or moderate mental retardation/learning disorder according to DSM-IV criteria. In the two studies, the response to risperidone at 0.02–0.06 mg/kg/day was significantly superior to that for the placebo on the pre-specified primary end point (i.e. the change

from baseline in the Conduct Problem subscale of the Nisonger-child behaviour rating form at week 6).[3]

Safety of risperidone according to prescribing information

Precautions[2,3]

- Risperidone may impair mental alertness.
- Elderly patients with dementia and who are treated with atypical antipsychotics have an increased risk of mortality.
- Risperidone should be used with caution in patients with risk factors for stroke.
- Owing to the alpha-blocking activity of risperidone, (orthostatic) hypotension may occur, especially during the initial dose titration period.
- Parkinson's disease may worsen with risperidone.
- Hyperglycaemia, diabetes mellitus and exacerbation of pre-existing diabetes have been reported during treatment with risperidone.
- Caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, especially during concomitant use of medicines known to prolong the QT interval.
- Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.
- Cases of venous thromboembolism have been reported with antipsychotic drugs.

Drug interactions

Possible interactions with other medicines are described in Table II.

Side effects

The most frequently reported side effects during clinical trials included the following:[2,3]

- parkinsonism
- sedation/somnolence
- headache
- insomnia.

Comparative safety data

Results from an open study comparing the efficacy and safety of olanzapine and risperidone in the treatment of elderly schizophrenia patients showed that both drugs were well tolerated. Their use was associated with fewer schizophrenic symptoms and less adverse effects than when the patients used a typical antipsychotic.[7]

Results from a randomised, double-blind, head-to-head clinical trial comparing the safety of aripiprazole and risperidone for treating autistic disorders showed no significantly different rate of adverse effects between the two groups. The safety and efficacy of aripiprazole (mean dose 5.5 mg/day) and risperidone (mean dose 1.12 mg/day) were comparable. The choice between these two medications should be made on the basis of clinical efficacy considering the patient's preference and clinical profile.[8]

Results from a study to evaluate the effects of risperidone compared with that of other atypical antipsychotics in treating patients with schizophrenia and schizophrenia-like psychosis showed that risperidone seems to produce more extrapyramidal side effects and a greater increase in prolactin than other second-generation ('atypical') antipsychotics.[9]

Important prescribing points[2,3]

- Risperidone is contraindicated in children under 5 years of

Table II: Interactions with other medicinal products[2,3]

Drug	Interacting effect	Points to consider
Alcohol, opiates, antihistamines and benzodiazepines	Increased risk of sedation	Use with caution in such combinations.
Levodopa and other dopamine agonists	Risperidone may antagonise the dopaminergic effect	If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.
Hypertensive treatment	Clinically significant hypotension has been observed	Caution is advised.
Furosemide	High incidence of mortality reported	Caution should be exercised and the risks and benefits of this combination should be considered.
Carbamazepine or other hepatic enzyme inducers	Decreased plasma levels of the active antipsychotic fraction of risperidone	On discontinuation the dosage of risperidone should be re-evaluated and, if necessary, decreased.
Fluoxetine and paroxetine	Plasma concentration of risperidone is increased owing to the CYP2D6-inhibiting effect of fluoxetine and paroxetine	When concomitant fluoxetine or paroxetine is initiated or discontinued, the dosage of risperidone should be re-evaluated.
Anti-arrhythmics (e.g. quinidine), tricyclic antidepressants (e.g. amitriptyline), tetracyclic antidepressants (e.g. maprotiline), some antihistamines, other antipsychotics and some antimalarials (e.g. quinine and mefloquine)	QT interval is prolonged	Caution is advised.

age, as efficacy and safety in young children have not been demonstrated.

- Owing to the alpha-blocking activity of risperidone, (orthostatic) hypotension may occur, especially during the initial dose titration period. Risperidone should be used with caution in patients with known cardiovascular disease and the dosage should be gradually titrated as recommended. A dose reduction should be considered if hypotension occurs.
- Doctors should consider the risks against the benefits when prescribing risperidone to patients with Parkinson's disease or dementia with Lewy bodies, as both patient groups may be at risk of neuroleptic malignant syndrome or have an increased sensitivity to antipsychotic medications.
- Caution should be exercised when risperidone is prescribed to patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome and during concomitant use with medicines known to prolong the QT interval.
- Before risperidone is prescribed to a child or adolescent with conduct disorder, the patient should be fully assessed for physical and social causes of the aggressive behaviour. The sedative effect of risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact on attention faculties of children and adolescents.

References

1. Janssen-Cilag. Data sheet: Risperidone. Janssen-Cilag (New Zealand). 11 Jul 2014. Available from: http://www.janssen.com/newzealand/sites/www_janssen_com_newzealand/files/prod_files/live/risperdaltabquickletssol.pdf
2. Janssen Pharmaceutica. Risperdal®. South African package insert. 24 Jun 2011.
3. Janssen-Cilag. Risperdal®. Electronic Medicines Compendium. 23 Jun 2015. Available from: http://www.medicines.org.uk/emc/medicine/30433
4. MIMS Australia. Risperidone. Drug info. Available from: www.emims.com.au
5. Himei A, Okamura T. Evaluation of the clinical efficacy of risperidone for untreated and treated cases of schizophrenia from various aspects. Psychiatry Clin Neurosci. 2005;59(5):556–562.
6. Vieta E. Acute and long-term treatment of mania. Dialogues Clin Neurosci. 2008; 10(2):165–179.
7. Ritchie CE, Chiu E, Harrigan S, et al. A comparison of the efficacy and safety of olanzapine and risperidone in the treatment of elderly patients with schizophrenia: an open study of six months duration. Int J Geriatr Psychiatry. 2006;21(2):171–179.
8. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. Child Psychiatry Hum Dev. 2014;45(2):185–192.
9. Komossa K, Rummel-Kluge C, Scwarz S, et al. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2011,Issue 1. Art. No.: CD006626. DOI: 10.1002/14651858.CD006626.pub2.