Risperdal

Pharmacology, Warnings, Pregnancy, Lactation, Side Effects, IV Compatibility, Dosage, Additional Dosage

Pharmacology (Top)

Pharmacology

Risperidone is a selective monoaminergic antagonist.

Risperidone specifically antagonizes serotonin Type 2 (5-HT2) receptors, dopamine Type 2 (D2) receptors, alpha-1 adrenergic receptors, and histaminic H1 receptors. Risperidone acts as an antagonist at other receptors, but with lower potency.

All forms of risperidone are approved by the FDA for use in the treatment of schizophrenia. Oral forms of risperidone are approved for use in the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder either as monotherapy or in combination with lithium or valproate and for irritability associated with Autistic Disorder, including symptoms of aggression towards others, deliberate self-harm, temper tantrums, and quickly changing moods. Risperidone long acting injection is approved by the FDA as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder.

Risperidone may prove useful in the patients with schizotypal personality disorder (SPD), borderline personality disorder, and severe tardive dyskinesia. Data from one study have suggested that risperidone is beneficial as an augmenting treatment in major depressive disorder patients who have developed high risk suicidal ideation during a depressive episode. Another study has reported that relative to baseline mood and drug craving status, risperidone was associated with depressive symptom improvement and reduced drug cravings. However, these uses have not been approved by the FDA and further clinical trials are needed before the drug can be recommended for these indications.

Pharmacokinetics

Risperidone is commercially available as a tablet, orally disintegrating tablet, oral solution, and long acting injection. The risperidone conventional tablets and orally disintegrating tablets were found to be bioequivalent.

The absolute oral bioavailability of risperidone is 70%. The relative oral bioavailability of risperidone from a tablet was 94% when compared to the solution.

The plasma protein binding averages 90% and is not significantly altered in patients with liver disease or renal dysfunction. The primary metabolite, 9-hydroxyrisperidone, is 77% bound to plasma proteins.

The volume of distribution averages 1.1 L/kg in both extensive metabolizers and poor metabolizers with normal renal and hepatic function.

The plasma clearance averages 5.4 mL/min/kg in extensive metabolizers with normal renal and hepatic function and 0.7 mL/min/kg in poor metabolizers with normal renal and hepatic function. The clearance of the sum of risperidone and its metabolites is decreased by approximately 60% in patients with moderate-to-severe renal dysfunction. This decrease has been found to be clinically significant for most patients with renal dysfunction. The renal clearance of risperidone and 9-hydroxyrisperidone has been reported to be decreased in elderly patients over the age of 65- years- old as compared to patients 65- years- old and younger. This decrease has been found to be clinically significant in most elderly patients.

The elimination half-life averages 3.2 hours in extensive metabolizers with normal renal and hepatic function and 19.2 hours in poor metabolizers with normal renal and hepatic function. The elimination half-life of risperidone and 9-hydroxyrisperidone has been reported to be increased in elderly patients over the age of 65- years- old as compared to patients 65- years- old and younger. This increased has been found to be clinically significant in most elderly patients.

Risperidone is metabolized in the liver to multiple metabolites, some of which are pharmacologically active. The principal metabolite is 9-hydroxyrisperidone and it exerts antipsychotic effects equivalent to those of risperidone. The metabolic conversion of risperidone to 9-hydroxyrisperidone is largely dependent on CYP450 2D6 (CYP450 3A4 and CYP450 3A5 are involved to a lesser extent). A mutation which occurs in approximately 7% of the white population can cause the conversion of risperidone to 9-hydroxyrisperidone to occur at a greatly reduced rate. Individuals who carry the mutation are called "poor- metabolizers". Although the pharmacokinetic disposition of risperidone is altered in poor metabolizers compared to extensive metabolizers, the pharmacokinetic disposition of the active moiety (i.e. the sum of risperidone and 9-hydroxyrisperidone) is not significantly changed.

In extensive metabolizers approximately 3% of a dose is recovered in the urine as intact drug and 35% as 9-hydroxyrisperidone. In poor metabolizers approximately 20% of a dose is recovered in the urine as intact drug and 10% is recovered in the urine as 9-hydroxyrisperidone.

There appears to be no change in the pharmacokinetic disposition of risperidone in patients with liver dysfunction compared to patients with normal liver function. However, the manufacturer reports a clinically significant increase of approximately 35% in the mean fraction of risperidone in patients with liver dysfunction due to the diminished concentration of both albumin and alpha-1- acid- glycoprotein in this population.

There are no data on the hemodialysis or peritoneal dialysis clearance of risperidone.

Warnings (Top)

(Severity: General Warning Exists)

Elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death. Trials in patients taking atypical antipsychotic drugs revealed a risk of death in drug treated patients of between 1.6 to 1.7 times the risk of death in placebo treated patients.

Neuroleptic Malignant Syndrome (NMS) has been reported with the use of antipsychotic agents. NMS is a potentially fatal symptom complex which may manifest as hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase (CPK), myoglobinuria, rhabdomyolysis, and acute renal failure.

Tardive dyskinesia may develop in patients treated with antipsychotic medications. Due to the severity of tardive dyskinesia, risperidone should be prescribed in such a way as to minimize any likely occurrence of tardive dyskinesia. In patients requiring chronic treatment, the smallest dose should be prescribed for the shortest duration of treatment producing a satisfactory response. Discontinuation of risperidone therapy, if feasible, should be considered if signs or symptoms of tardive dyskinesia appear.

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone.

Risperidone is associated with hyperprolactinemia. Because about one-third of human breast cancers are prolactin-dependent in vitro, caution should be used if risperidone therapy is contemplated for a patient with a history of breast cancer.

Risperidone may precipitate orthostatic hypotension, associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose titration period, probably reflecting its alpha-adrenergic antagonistic properties.

Leucopenia/neutropenia and agranulocytosis have been reported temporally related to antipsychotic agents. Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of risperidone should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm3) should discontinue risperidone and have their WBC followed until recovery.

Somnolence is commonly reported in patients on risperidone. Risperidone may impair the mental abilities necessary for potentially hazardous tasks such as driving or operating machinery.

Risperidone should be used with caution in patients with a seizure disorder or during alcohol withdrawal or myelography because it may lower the seizure threshold.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Priapism has been reported during postmarketing surveillance.

Disruption of body temperature regulation has been attributed to antipsychotic agents. Hyperthermia and hypothermia have both been reported in association with risperidone. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Patients with phenylketonuria should be informed that orally disintegrating tablets contain phenylalanine. Risperidone should not be administered in the presence of large amounts of other CNS depressants.

Risperidone, like phenothiazine antipsychotics, should be administered with caution to patients with cardiovascular disease, severe respiratory disease, acute undiagnosed abdominal pain, severe renal disease, severe liver disease, Parkinson's disease, dementia with Lewy bodies, prostatic hypertrophy, urethral stricture, and glaucoma.

Suicide is an inherent risk in any patient with schizophrenia. High-risk patients should be closely supervised while receiving risperidone therapy.

The risperidone long acting intramuscular formulation should be administered into the gluteal muscle with careful avoidance of inadvertent injection into the vasculature.

FDA notified healthcare professionals and the public of medication error reports in which patients were given risperidone (Risperdal [R]) instead of ropinirole (Requip [R]) and vice versa.

Pregnancy (Top)

(Severity: Major Female, Minor Male Pregnancy Warning)

Risperidone has been assigned to pregnancy category C by the FDA. Animal studies have revealed evidence of embryolethality (possibly due to maternal toxicity) but have failed to reveal evidence of teratogenicity. There are no controlled data in human pregnancy. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in human neonates following in utero exposure to antipsychotics in the third trimester. Risperidone is only recommended for use during pregnancy when there are no alternatives and benefit outweighs risk.

Hyperprolactinemia caused by risperidone may impair reproductive function in both male and female patients. Hyperprolactinemia causes a reduction in the pituitary secretion of gonadotropin which, in turn, impairs gonadal steroidogenesis.

Lactation (Top)

(Severity: Minor Lactation Warning)

Risperidone and its active 9-hydroxymetabolite are excreted into human milk. The manufacturer recommends that due to the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Additionally, women should not breast-feed during treatment with risperidone long-acting injection and for at least 12 weeks after the last injection.

Side Effects (Top)

Nervous system

Nervous system side effects have frequently included insomnia (26%), dystonia (18%), akathisia (16%), extrapyramidal symptoms (17%), headache (14%), dizziness (11%), parkinsonism (6%), asthenia (4%), somnolence (3%), and hypoesthesia (2%). Increased dream activity, nervousness, impaired concentration, increased sleep duration, dysarthria, vertigo, stupor, paraesthesia, confusion, and amnesia have also been reported. Delirium, withdrawal syndrome, yawning, aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis, seizures, neuroleptic malignant syndrome, tardive dyskinesia, and sleep related eating disorder (SRED) have been reported rarely. Head titubation and dysgeusia have also been reported.

Cardiovascular

Cardiovascular side effects have frequently included tachycardia, hypertension, and hypotension. Palpitation, AV block, and myocardial infarction have also been reported. Ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, syncope, edema, ST depression, myocarditis, venous thromboembolism, and bradycardia have been reported rarely. Prolongation of the QT interval has been reported in some patients. One fatal cardiac event following initiation of risperidone therapy has been reported.

Cerebrovascular events (e.g., stroke and transient ischemic attack), including fatalities, have rarely been reported and then primarily in elderly patients with dementia- related psychosis.

An increased risk of mortality, possibly due to heart failure or sudden death, has been reported with the use of atypical antipsychotic agents, including risperidone, in the treatment of behavioral disorders in the elderly patient with dementia. However, it should be noted that conflicting data exist regarding an increased risk of mortality and use of risperidone in elderly dementia patients.

During postmarketing surveillance, retinal artery occlusion in the presence of abnormal arteriovenous anastomosis has been reported following injection of long-acting risperidone.

Endocrine

Endocrine side effects have included hyperprolactinemia, diabetes, and antidiuretic hormone disorder. Compared with other antipsychotic drugs, risperidone is associated with a greater elevation in prolactin levels.

Genitourinary

Genitourinary side effects have frequently included urinary incontinence, polyuria, and polydipsia. Hematuria and dysuria have also been reported. Urinary retention, gynecomastia, and cystitis have been reported rarely. Menorrhagia, galactorrhea, orgastic dysfunction, dry vagina, nonpuerperal lactation, amenorrhea, breast pain, leukorrhea, mastitis, dysmenorrhea, perineal pain, intermenstrual bleeding, and vaginal hemorrhage have been reported in females. Erectile dysfunction, ejaculation failure, breast pain, and priapism have been reported in males. Hyperprolactinemia caused by risperidone may impair reproductive function in both male and female patients. Hyperprolactinemia causes a reduction in the pituitary secretion of gonadotropin which, in turn, impairs gonadal steroidogenesis.

Gastrointestinal

Gastrointestinal side effects have frequently included constipation, nausea, dyspepsia, vomiting, abdominal pain, tooth ache, tooth disorder, dry mouth, and hypersalivation. Anorexia, hyposalivation, flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, and gastritis have also been reported. Fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, gastrointestinal hemorrhage, bitter taste, and hematemesis have also been reported.

Hepatic

Hepatic side effects have included mild reversible elevations in liver function tests, including SGOT and SGPT. Hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, and hepatocellular damage have been reported rarely.

Psychiatric

Psychiatric side effects have frequently included agitation, anxiety, manic reaction, and aggressive reaction. Diminished sexual desire, depression, apathy, catatonic reaction, euphoria, and increased libido have also been reported. Emotional lability, nightmares, and obsessive-compulsive symptoms have been reported rarely.

Ocular

Ocular side effects have frequently included abnormal vision. Abnormal accommodation and xerophthalmia

have also been reported. Diplopia, eye pain, blepharitis, photopsia, photophobia, and abnormal lacrimation have been reported rarely. A case of periorbital edema has also been reported.

Metabolic

Metabolic side effects have frequently included weight gain. Hyponatremia, creatine phosphokinase increase, thirst, weight decrease, and hyperglycemia have also been reported. Decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, and hypoglycemia have been reported rarely. A large scale clinical trial at clinically relevant doses has reported significant reductions in glucose tolerance during treatment with risperidone.

Respiratory

Respiratory side effects have frequently included rhinitis, coughing, sinusitis, pharyngitis, upper respiratory infection, and dyspnea. Hyperventilation, bronchospasm, pneumonia, and stridor have also been reported. Asthma, increased sputum, and aspiration have been reported rarely. A case of respiratory dyskinesia has also been reported.

An increased risk of mortality, possibly due to an infection such as pneumonia, has been reported with the use of atypical antipsychotic agents, including risperidone, in the treatment of behavioral disorders in the elderly patient with dementia.

Postmarketing experience has included sleep apnea syndrome.

Other 1

Other side effects have frequently included back pain, chest pain, fever, pain, fatigue, and injury. Edema, rigors, malaise, and influenza-like symptoms have also been reported. Pallor, enlarged abdomen, ascites, sarcoidosis, flushing, tinnitus, hyperacusis, decreased hearing, and nose bleeds have been reported rarely. Postmarketing experience has included hypothermia and pyrexia.

Dermatologic

Dermatologic side effects have frequently included rash, dry skin, seborrhea, acne, pruritus, increased pigmentation, and photosensitivity. Increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, and skin exfoliation have also been reported. Bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, and urticaria have been reported rarely.

Musculoskeletal

Musculoskeletal side effects have frequently included arthralgia, myalgia, and skeletal pain. Arthrosis, synostosis, bursitis, arthritis, and skeletal pain have been reported rarely. Decreased bone density may occur in both male and female patients as a result of risperidone- induced prolonged hyperprolactinemia. A case of Pisa syndrome has also been reported.

Renal

Renal side effects have rarely included renal insufficiency.

Hypersensitivity

Hypersensitivity side effects have rarely included allergic reaction.

Hematologic

Hematologic side effects have rarely included epistaxis, purpura, hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia, anemia, hypochromic anemia, normocytic anemia, leukocytosis, lymphadenopathy, leukopenia, and Pelger Huët anomaly. Neutropenia has also been reported

Immunologic

Immunologic side effects have included one case of risperidone induced erythema multiforme minor and a case of immuno allergic hepatitis.

Extrapyramidal symptoms may be less frequently associated with risperidone than most other available antipsychotics. Treatment of extrapyramidal effects, in addition to general supportive measures, may include judicious use of one or more of the following: benztropine, trihexyphenidyl, biperiden, or diphenhydramine.

Sedation may occur, particularly at higher doses. Blurred vision, vertigo, impaired concentration, increased appetite and decreased appetite have also been reported.

At least three cases of tardive dyskinesia have also been reported with risperidone use with one case accompanied by risperidone induced parkinsonism. Tardive dyskinesia involves involuntary, dyskinetic, repetitive movements. Tardive dyskinesia may be irreversible and is related to both the duration of therapy and the total amount of drug consumed. Frequent discontinuation and resumption of therapy may predispose patients to the development of tardive dyskinesia.

At least fourteen cases of neuroleptic malignant syndrome have been reported with risperidone use. Fever, altered consciousness, autonomic dysfunction and muscle rigidity are the hallmarks of the neuroleptic malignant syndrome. The neuroleptic malignant syndrome is associated with a case fatality rate of about 20%. Immediate discontinuation of neuroleptic therapy, consideration of dantrolene administration as well as intensive monitoring and supportive care are indicated. Nine of the 13 cases reported were between 15 and 43 years old. One of the cases had a delayed onset and another case resulted in death.

One study has reported that in patients who were given risperidone, there was a positive correlation between improvement in psychopathology and improvement in cognitive test of explicit memory and alertness.

Collective data gathered from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including risperidone, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug- treated patient than in the placebo- treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Similar results (i.e., increased risk of mortality with atypical antipsychotics) were reported in another meta-analysis involving elderly dementia patients that consisted of 15 randomized, placebo-controlled trials (n=3353) of 10 to 12 weeks in duration. Risperidone is not approved by the FDA for use in the treatment of behavioral disorders in elderly patients with dementia. However, in contrast, the results of another meta-analysis of 6 randomized, double-blind, placebo-controlled, clinical trials (n=1721) found a nonsignificant increase in overall mortality in elderly dementia patients treated with risperidone.

The results of a large retrospective cohort study appear to indicate that atypical antipsychotic agents (i.e., risperidone, olanzapine, clozapine, quetiapine) increase the risk of venous thromboembolism in elderly patients; however, these events seem to be rare.

Based on data from four placebo controlled trials conducted in elderly patients (n=1230), cerebrovascular

adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in elderly patients with dementia- related psychosis. In placebo controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. Risperidone has not been shown to be safe or effective in the treatment of patients with dementia- related psychosis. Additional information on these and other clinical trials conducted in elderly patients can be obtained by calling 1-800- JANSSEN (800-526-7736). However, the association between the use of atypical antipsychotics (i.e., risperidone, olanzapine) and the risk of cerebrovascular events appears to be somewhat controversial. The results of a case-control study found no increased risk of cerebrovascular events in elderly patients treated with atypical antipsychotics.

Hyperprolactinemia in some patients may cause sexual dysfunction (i.e., decreased libido, impaired performance), gynecomastia, reduced fertility, galactorrhea, menstrual irregularities (i.e., amenorrhea, oligomenorrhea), and osteoporosis. In addition, as many as one-third of human breast cancers may be prolactin-dependent in vitro. Treatment of risperidone- induced hyperprolactinemia may include use of bromocriptine, amantadine, or cabergoline as well as discontinuation of therapy.

A study of U.S. military veterans with schizophrenia has reported that patients on risperidone had 1.49 times as many cases of diabetes when compared to patients taking decades old drugs for psychosis including haloperidol, thioridazine, and others. Additional studies have confirmed that patients receiving atypical antipsychotics (i.e., clozapine, risperidone, olanzapine, quetiapine, ziprasidone) are at an increased risk of developing hyperglycemia and/or diabetes mellitus.

A case of priapism lasting approximately 36- hours in duration was reported in a 32- year- old male approximately 8 weeks after initiation of risperidone for the treatment of schizophrenia and 2 weeks after an increase in daily dosage to 5 mg. Risperidone was discontinued immediately. The patient reported, after this event, that he had been experiencing prolonged erections since initiation of risperidone therapy, a phenomenon commonly reported with priapism. However, the patient did not report these events to his clinicians until after this event.

Approximately 18 cases of risperidone- associated priapism have been reported, including a patient who developed priapism while being switched from the oral to the intramuscular formulation. Risperidone- induced priapism is believed to be caused by alpha-adrenergic blockade.

At least one case of rapid onset risperidone induced hepatotoxicity has been reported.

A 30-year-old patient experienced acute symptoms of cholestasis after 8 years of risperidone therapy. Once the drug was discontinued, the symptoms resolved completely. Eleven months later, quetiapine was introduced and the patient once again developed acute symptoms of cholestasis which later resolved after quetiapine discontinuation.

Ocular side effects were looked at in one study on the adverse effects of risperidone on eye movement. The study reported a prolonged latency and decreased peak velocity and accuracy of saccadic eye movements that was detectable four weeks after treatment initiation.

The results of the large scale clinical trial noted that treatment related changes in glucose tolerance were largely explained by changes in insulin sensitivity.

Hyperglycemia has been reported in some cases to be extreme and associated with ketoacidosis or hyperosmolar coma and death.

Treatment with risperidone has been associated with moderate weight gain (mean 2.1 kg). Risperidone-associated weight gain appears to be more pronounced in the young, males, non- white race, and those with a

lower body mass index.

Collective data gathered from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including risperidone, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug- treated patient than in the placebo- treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Risperidone is not approved by the FDA for use in the treatment of behavioral disorders in elderly patients with dementia.

A case of respiratory dyskinesia characterized by involuntary movements of the respiratory musculature, irregular respiration, grunting, and hyperventilation was reported in a patient following discontinuation of risperidone. Symptoms resolved after restarting risperidone and subsequently, were less severe with a more gradual withdrawal of risperidone.

IV Compatibility

Dosage (Top)

Usual Adult Dose

Schizophrenia

Initial dose: 1 mg orally twice a day
Titration dose: May increase in increments of 1 mg twice daily on the second and third day. Dosage adjustments after the third day should be done in one week intervals.
Maximum dose: 16 mg per day

Injection:
For patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone long acting injection.

25 mg every 2 weeks by deltoid or deep IM gluteal injection.

Although dose response for effectiveness has not been established for risperidone long acting injection, some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks. When clinical factors warrant a dose adjustment, such as in patients with hepatic or renal dysfunction or a possible drug interaction, a lower initial dose of 12.5 mg may be appropriate; however, the efficacy of the 12.5 mg dose has not been studied in clinical trials.

Oral risperidone (or another antipsychotic medication) should be given with the first injection and continued for 3 weeks to ensure adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection.

Bipolar Disorder

Long-acting injection:
For monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder:

Recommended dose: 25 mg IM every 2 weeks. Some patients may benefit from a higher dose of 37.5 mg or 50 mg.

Dosages above 50 mg have not been studied in this population.

Risperidone long-acting injection for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Oral:
For use in the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder:

Initial Dose: 2 or 3 mg orally once a day.

If needed, dosage adjustments should occur at intervals of not less than 24 hours in dosage increments/decrements of 1 mg per day.

Clinical trials for short-term (3 week) antimanic use have reported efficacy at a dosage range of 1 to 6 mg per day. Dosages above 6 mg per day have not been studied.

Usual Geriatric Dose

Bipolar Disorder

For use in the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder:

Initial Dose: 0.5 mg twice a day

If needed, dosage adjustments should occur at intervals of not less than 24 hours in dosage increments/decrements of 1 mg per day.

Clinical trials for short-term (3 week) anti- manic use have reported efficacy at a dosage range of 1 to 6 mg per day. Dosages above 6 mg per day have not been studied.

Note: Use of the long acting injectable form of risperidone is not recommended for this indication.

Schizophrenia

Initial dose: 0.5 mg orally twice a day.
Maintenance dose: May increase in 0.5 mg twice a day increments. Dosage increases greater than 1.5 mg per day should be done at greater than 1 week intervals.

Many clinicians recommend a daily dosage of 0.5 to 2 mg in elderly patients for the treatment of schizophrenia. The incidence of side effects, especially extrapyramidal symptoms, has been reported to be increased with doses of 2 mg or greater per day in this population.

Injection:
For patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone long acting injection.

25 mg every 2 weeks by deep IM gluteal injection.

Oral risperidone (or another antipsychotic medication) should be given with the first injection and continued for 3 weeks to ensure adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection.

Usual Pediatric Dose

Autism

Risperidone is approved by the FDA for use in pediatric patients for the treatment of irritability associated with autistic disorder in children and adolescents:

5 years to 18 years; 15 kg to 19 kg body weight:
Initial dose: 0.25 mg orally once a day (or 0.125 mg orally twice a day) for a minimum duration of 4 days
Maintenance dose: 0.5 mg orally once a day (or 0.25 mg orally twice a day) for a minimum duration of 14 days. Then, if necessary, the dose may be titrated upwards in increments of no more than 0.25 mg per day at 2 week intervals.
Maximum recommended dose: 1 mg orally per day

5 years to 18 years; 20 kg to 39 kg body weight:
Initial dose: 0.5 mg orally once a day (or 0.25 mg orally twice a day) for a minimum duration of 4 days
Maintenance dose: 1 mg orally once a day (or 0.5 mg orally twice a day) for a minimum duration of 14 days. Then, if necessary, the dose may be titrated upwards in increments of no more than 0.5 mg per day at 2 week intervals.
Maximum recommended dose: 2.5 mg orally per day (3 mg/day in children over 45 Kg).

5 years to 18 years; at least 40 kg:
Initial dose: 0.5 mg orally once a day (or 0.25 mg orally twice a day) for a minimum duration of 4 days
Maintenance dose: 1 mg orally once a day (or 0.5 mg orally twice a day) for a minimum duration of 14 days. Then, if necessary, the dose may be titrated upwards in increments of no more than 0.5 mg per day at 2 week intervals.
Maximum recommended dose: 3 mg orally per day

Once sufficient clinical response is achieved, clinicians may want to consider a gradual reduction in dose keeping in mind the optimal balance of safety and efficacy.

Bipolar Disorder

Risperidone is approved by the FDA for use in pediatric patients for the treatment of bipolar mania in children and adolescents:

10 to 17 years:
Initial dose: 0.5 mg once a day
Maintenance dose: Initial dose may be titrated upwards to a maximum recommended dose of 2.5 mg per day. If necessary, upward titration may occur in increments of 0.5 to 1 mg per day at intervals not less than 24 hours.

There are data from clinical studies supporting efficacy in doses up to 6 mg per day in pediatric patients with bipolar mania. However, no additional benefit was observed in doses greater than 2.5 mg per day. In addition, higher doses have been associated with more adverse effects.

Schizophrenia

Risperidone is approved by the FDA for use in the treatment of schizophrenia in adolescents:

13 to 17 years:
Initial dose: 0.5 mg orally once a day
Titrated dose: Initial dose may be titrated upwards in increments of 0.5 to 1 mg per day at intervals not less

than 24 hours
Maintenance dose: 3 mg per day
Doses up to 6 mg per day have been studied in the treatment of schizophrenia in adolescents. However, no additional benefit was observed at doses greater than 3 mg per day.

There are no clinical data regarding the use of risperidone in adolescents with schizophrenia for periods exceeding 8 weeks.

Other

Pervasive Developmental Disorders:
6 to 12 years:
Initial dose: 0.5 mg orally per day
Maintenance: titrate up to 0.75 to 3 mg orally per day

Tourette's Syndrome:
6 to 18 years:
Initial dose: 0.5 mg orally per day
Maintenance dose: Titrate as needed up to 2 to 4 mg per day

Additional Dosage (Top)

Renal Dose Adjustments

Oral:
Initial dose: 0.5 mg orally twice a day.
Maintenance dose: May increase in 0.5 mg twice a day increments. Dosage increases greater than 1.5 mg/day should be done at greater than 1 week intervals.

Injection:
If a total daily dose of at least 2 mg orally is well tolerated, the long acting intramuscular formulation may be used.

Initial dose: 25 mg every 2 weeks by deep IM gluteal injection.

A starting dose of 12.5 mg IM may be considered when clinical factors warrant a dose adjustment; however, it should be noted that the efficacy of the 12.5 mg dose has not been studied in clinical trials.

Liver Dose Adjustments

Oral:
Initial dose: 0.5 mg orally twice a day.
Maintenance dose: May increase in 0.5 mg twice a day increments. Dosage increases greater than 1.5 mg per day should be done at greater than 1 week intervals.

Injection:
If a total daily dose of at least 2 mg orally is well tolerated, the long acting intramuscular formulation may be used.

Initial dose: 25 mg every 2 weeks by deep IM gluteal injection.

A starting dose of 12.5 mg IM may be considered when clinical factors warrant a dose adjustment; however, it

should be noted that the efficacy of the 12.5 mg dose has not been studied in clinical trials.

Dose Adjustments

A reduction in the initial dosage and a slower titration may be necessary in patients who are debilitated, predisposed to hypotension, or hypotension would pose a risk.

Precautions

Risperidone is not approved by the FDA for use in the treatment of behavioral disorders in elderly patients with dementia. Collective data from 17 placebo-controlled clinical studies (n=5106) involving the use of atypical antipsychotic agents, including risperidone, for the treatment of behavioral disorders in the elderly patient with dementia showed a risk of death 1.6 to 1.7 times greater in the drug- treated patient than in the placebo- treated patient. The average length of duration for the trials was 10 weeks with the cause of death in the majority of cases, though not all, reported as either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In addition, based on data from four placebo controlled trials conducted in elderly patients (n=1230), cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in elderly patients with dementia- related psychosis. In placebo controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. Risperidone has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis. Additional information on these and other clinical trials conducted in elderly patients can be obtained by calling 1-800- JANSSEN (800-526-7736).

The risperidone long acting intramuscular formulation should be administered into the gluteal muscle with careful avoidance of inadvertent injection into the vasculature.

Safety and effectiveness of the risperidone long acting intramuscular formulation have not been established in pediatric patients (less than 18 years of age).

Dialysis

Data not available

Other Comments

Doses greater than 6 mg per day are associated with more adverse effects and are generally not recommended, but may be necessary in some patients.

Risperidone induced hyperprolactinemia may be especially detrimental to pediatric patients as it may possibly result in irreversible hypogonadism and osteoporosis.

The therapeutically effective risperidone plasma concentration range is 20 to 60 ng/mL. Plasma concentrations above 74 ng/mL appear to be associated with parkinsonian adverse effects.

Development of hyperglycemia and/or diabetes mellitus is common in patients treated with atypical antipsychotics. Periodic monitoring of fasting plasma glucose is recommended in patients receiving risperidone.